FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	PF-0733 USN
	U.S. APPLICATION NO. (if known, see 37 CFR 1.5) TO BE ASSIGNED 09/018170

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US00/16636	16 June 2000	16 June 1999

TITLE OF INVENTION
INTRACELLULAR SIGNALING MOLECULES

APPLICANT(S) FOR DO/EO/US
YUE, Henry; TANG, Y. Tom; HILLMAN, Jennifer L.; LAL, Preeti; BANDMAN, Olga; BAUGHN, Mariah R.; AZIMZAI, Yalda; YANG, Junming; REDDY, Roopa, LU, Dyung Aina M.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is the **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to promptly begin national examination procedures (35 U.S.C. 371 (f)).
4. ☐ The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau)
   b. ☐ has been communicated by the International Bureau.
   c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
   e. ☒ attached hereto Article 34 Amendment
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 16 below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.27 and 3 31 is included
13. ☒ A FIRST preliminary amendment, as follows:
    Cancel in this application original claims #12, 14, 18, 20, 21, 23, 24, 25, 28-204 before calculating the filing fee, without prejudice or disclaimer. Applicants submit that these claims were included in the application as filed in the interest of providing notice to the public of certain specific subject matter intended to be claimed, and are being canceled at this time in the interest of reducing filing costs. Applicants expressly state that these claims are not being canceled for reasons related to patentability, and are in fact fully supported by the specification as filed. Applicants expressly reserve the right to reinstate these claims or to add other claims during prosecution of this application or a continuation or divisional application. Applicants expressly do not disclaim the subject matter of any invention disclosed herein which is not set forth in the instantly filed claims.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:
1) Transmittal Letter (2 pp, in duplicate)
2) Return Postcard
3) Express Mail Label No.: **EL 856148931 US**
4) Sequence Listing Statement

U.S. APPLICATION NO (if known, see 37 CFR 1 5) TO BE ASSIGNED 10/018170	INTERNATIONAL APPLICATION NO.: PCT/US00/16636	ATTORNEY'S DOCKET NUMBER PF-0733 USN

17 ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5):

Neither international preliminary examination fee (37 CFR 1 482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO . $1000 00

☐International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO..$860 00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1 445(a)(2)) paid to USPTO.....$710.00

☒**International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4).....$710.00**

☐International preliminary examination fee paid to USPTO (37 CFR 1 482) and all claims satisfied provisions of PCT Article 33(1)-(4). $100 00

ENTER APPROPRIATE BASIC FEE AMOUNT =				$710.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1 492(e))				$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	19 =	0	X **$ 18.00**	$	
Independent Claims	2 =	0	X **$ 80.00**	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$270.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$	
☐ Applicant claims small entity status. See 37 CFR 1 27 The fees indicated above are reduced by 1/2				$	
SUBTOTAL =				$710.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1492(f)). +				$	
TOTAL NATIONAL FEE =				$710 00	
Fee for recording the enclosed assignment (37 CFR 1 21(h)) The assignment must be accompanied by the appropriate cover sheet (37 CFR 3 28, 3 31) **$40.00** per property +					
TOTAL FEES ENCLOSED =				$710 00	
				Amount to be Refunded	$
				Charged	$

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed

b. ☒ Please charge my Deposit Account No 09-0108 in the amount of $710 00 to cover the above fees

c ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No 09-0108 A duplicate copy of this sheet is enclosed

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

INCYTE GENOMICS, INC
3160 Porter Drive
Palo Alto, CA 94304

SIGNATURE

NAME: Diana Hamlet-Cox

REGISTRATION NUMBER. 33,302

DATE. 11 December 2001

10/018170

Docket No.: PF-0733 USN

"Express Mail" mailing label number EL 856148931 US. I hereby certify that this document and referenced attachments are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR § 1.10, addressed to: Commissioner for Patents, Box Patent Application, 2900 Crystal Drive, Arlington, VA 22202-3513 on 11 December 2001.

By: Nancy Ramos Printed: NANCY RAMOS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Yue et al.

Title: INTRACELLULAR SIGNALING MOLECULES

PCT Serial No.: PCT/US00/16636 International Filing Date: 16 June 2000

Examiner: To Be Assigned Group Art Unit: To Be Assigned

Assistant Commissioner for Patents
Box Patent Application
Washington, D.C. 20231

SUBMISSION UNDER 37 CFR § 1.821-1.825 SEQUENCE LISTING

Sir:

In accordance with the requirements of 37 CFR § 1.821-1.825, Applicants hereby submit one (1) diskette(s) containing the computer-readable information for the Sequence Listing of the above-identified application. The content of the Sequence Listing paper copy is identical to the computer-readable copy filed with the US Receiving Office. The USPTO is authorized to add whatever is necessary to update the CRF with the current application information.

Respectfully submitted,

INCYTE GENOMICS, INC.

Date: 11 December 2001

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10018170 121101
10/018170
JC05 Rec'd PCT/PTO 11 DEC 2001

Docket No.: PF-0733 USN

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231
on 12-11-01
By: Mona Ramos
Printed: Mona Ramos

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Yue, et al.

Title: HUMAN INTRACELLULAR SIGNALING MOLECULES

PCT Serial No.: PCT/US00/16636 International Filing Date: 16 June 2000

Examiner: To Be Assigned Group Art Unit: To Be Assigned

Commissioner for Patents
BOX PATENT APPLICATION
Washington, D.C. 20231

REQUEST TO PUBLISH APPLICATION WITH ARTICLE 34 AMENDMENTS

Sir:

Applicants respectfully request that the present application be published under 35 U.S.C. § 122(b) with the claims as amended under PCT Article 34 on the attached substitute sheets, and which are submitted with the attached PCT application, rather than as originally filed.

Applicants submit that the Article 34 amendments should be considered as a part of the application as filed, as they were submitted in the form of replacement sheets during Chapter II examination of the PCT application, and should not be considered as a preliminary amendment which cannot be published unless submitted in electronic form.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108. This form is enclosed in duplicate.**

Respectfully submitted,
INCYTE GENOMICS, INC.

Date: 11 Dec 2001

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INTRACELLULAR SIGNALING MOLECULES

TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of intracellular signaling molecules and to the use of these sequences in the diagnosis, treatment, and prevention of cell proliferative, autoimmune/inflammatory, neurological, gastrointestinal, reproductive, and developmental disorders.

BACKGROUND OF THE INVENTION

Cell-cell communication is essential for the growth, development, and survival of multicellular organisms. Cells communicate by sending and receiving molecular signals. An example of a molecular signal is a growth factor, which binds and activates a specific transmembrane receptor on the surface of a target cell. The activated receptor transduces the signal intracellularly, thus initiating a cascade of biochemical reactions that ultimately affect gene transcription and cell cycle progression in the target cell.

Intracellular signaling is the process by which cells respond to extracellular signals (hormones, neurotransmitters, growth and differentiation factors, etc.) through a cascade of biochemical reactions that begins with the binding of a signaling molecule to a cell membrane receptor and ends with the activation of an intracellular target molecule. Intermediate steps in the process involve the activation of various cytoplasmic proteins by phosphorylation via protein kinases, and their deactivation by protein phosphatases, and the eventual translocation of some of these activated proteins to the cell nucleus where the transcription of specific genes is triggered. The intracellular signaling process regulates all types of cell functions including cell proliferation, cell differentiation, and gene transcription, and involves a diversity of molecules including protein kinases and phosphatases, and second messenger molecules such as cyclic nucleotides, calcium-calmodulin, inositol, and various mitogens that regulate protein phosphorylation.

Intracellular signaling is carried out by a variety of molecules that promote the transduction and amplification of the signal. For example, binding of a ligand to a transmembrane receptor activates membrane-associated intracellular proteins, such as G-proteins. G-proteins mediate both the level of intracellular second messengers, such as cyclic AMP, and the activity of signaling enzymes, such as phospholipase C. These messengers and enzymes then activate signal transduction pathways, many of which are mediated by protein kinase cascades. Phosphorylation of proteins in response to extracellular signals, cell cycle checkpoints, and environmental or nutritional stresses is often accomplished by transfer of a high energy phosphate from ATP. Second messengers whose effects are mediated by protein kinases include cyclic AMP, cyclic GMP, inositol triphosphate, cyclic ADP

ribose, and calcium/calmodulin. Alternatively, binding of ligand to a transmembrane receptor, such as a receptor tyrosine kinase, triggers the activation of a molecular "switch," such as a monomeric GTPase. In this case, binding of ligand to the receptor activates a catalytic domain in the intracellular portion of the receptor. This activated domain then switches on the activity of monomeric GTPases such as Ras, usually via adaptor proteins.

Cells also respond to changing conditions by switching off signals. Many signal transduction proteins are short-lived and rapidly targeted for degradation by covalent ligation to ubiquitin, a highly conserved small protein. Cells also maintain mechanisms to monitor changes in the concentration of denatured or unfolded proteins in membrane-bound extracytoplasmic compartments, including a transmembrane receptor that monitors the concentration of available chaperone molecules in the endoplasmic reticulum and transmits a signal to the cytosol to activate the transcription of nuclear genes encoding chaperones in the endoplasmic reticulum.

Certain proteins in intracellular signaling pathways serve to link or cluster other proteins involved in the signaling cascade. These proteins are referred to as scaffold, anchoring, or adaptor proteins. (For review, see Pawson, T., and Scott, J.D. (1997) Science 278:2075-2080.) As many intracellular signaling proteins such as protein kinases and phosphatases have relatively broad substrate specificities, the adaptors help to organize the component signaling proteins into specific biocehmical pathways.

Gangliosides, generally associated with plasma membranes, also participate in signal transduction. Aberrant ganglioside function has been implicated in inflammatory and degenerative diseases within and outside of the nervous system, including Tay-Sachs disease, multiple sclerosis, lupus erythematosus, and insulin-dependent diabetes mellitus (Misasi, R. et al. (1997) Diabetes Metab. Rev. 13:163-179).

Many of the above signaling molecules are characterized by the presence of particular domains that promote protein-protein interactions. A sampling of these domains is discussed below, along with other important intracellular messengers.

Intracellular Signaling Second Messenger Molecules

Phospholipid and Inositol-phosphate Signaling

Inositol phospholipids (phosphoinositides) are involved in an intracellular signaling pathway that begins with binding of a signaling molecule to a G-protein linked receptor in the plasma membrane. This leads to the phosphorylation of phosphatidylinositol (PI) residues on the inner side of the plasma membrane to the biphosphate state (PIP_2) by inositol kinases. Simultaneously, the G-protein linked receptor binding stimulates a trimeric G-protein which in turn activates a phosphoinositide-specific phospholipase C-β. Phospholipase C-β then cleaves PIP_2 into two

products, inositol triphosphate (IP_3) and diacylglycerol. These two products act as mediators for separate signaling events. IP_3 diffuses through the plasma membrane to induce calcium release from the endoplasmic reticulum (ER), while diaacylglycerol remains in the membrane and helps activate protein kinase C, an STK that phosphorylates selected proteins in the target cell. The calcium response initiated by IP_3 is terminated by the dephosphorylation of IP_3 by specific inositol phosphatases. Cellular responses that are mediated by this pathway are glycogen breakdown in the liver in response to vasopressin, smooth muscle contraction in response to acetylcholine, and thrombin-induced platelet aggregation.

Cyclic Nucleotide Signaling

Cyclic nucleotides (cAMP and cGMP) function as intracellular second messengers to transduce a variety of extracellular signals including hormones, light, and neurotransmitters. In particular , cyclic-AMP dependent protein kinases (PKA) are thought to account for all of the effects of cAMP in most mammalian cells, including various hormone-induced cellular responses. Visual excitation and the phototransmission of light signals in the eye is controlled by cyclic-GMP regulated, Ca^{2+}-specific channels. Because of the importance of cellular levels of cyclic nucleotides in mediating these various responses, regulating the synthesis and breakdown of cyclic nucleotides is an important matter. Thus adenylyl cyclase, which synthesizes cAMP from AMP, is activated to increase cAMP levels in muscle by binding of adrenaline to β-andrenergic receptors, while activation of guanylate cyclase and increased cGMP levels in photoreceptors leads to reopening of the Ca^{2+}-specific channels and recovery of the dark state in the eye. In contrast, hydrolysis of cyclic nucleotides by cAMP and cGMP-specific phosphodiesterases (PDEs) produces the opposite of these and other effects mediated by increased cyclic nucleotide levels. PDEs appear to be particularly important in the regulation of cyclic nucleotides, considering the diversity found in this family of proteins. At least seven families of mammalian PDEs (PDE1-7) have been identified based on substrate specificity and affinity, sensitivity to cofactors, and sensitivity to inhibitory drugs (Beavo, J.A. (1995) Physiological Reviews 75:725-48). PDE inhibitors have been found to be particularly useful in treating various clinical disorders. Rolipram, a specific inhibitor of PDE4, has been used in the treatment of depression, and similar inhibitors are undergoing evaluation as anti-inflammatory agents. Theophylline is a nonspecific PDE inhibitor used in the treatment of bronchial asthma and other respiratory diseases (Banner, K.H. and Page, C.P. (1995) Eur. Respir. J. 8:996-1000).

Calcium Signaling Molecules

Ca^{+2} is another second messenger molecule that is even more widely used as an intracellular mediator than cAMP. Two pathways exist by which Ca^{+2} can enter the cytosol in response to extracellular signals: One pathway acts primarily in nerve signal transduction where Ca^{+2} enters a nerve terminal through a voltage-gated Ca^{+2} channel. The second is a more ubiquitous pathway in

which Ca^{+2} is released from the ER into the cytosol in response to binding of an extracellular signaling molecule to a receptor. Ca^{2+} directly activates regulatory enzymes, such as protein kinase C, which trigger signal transduction pathways. Ca^{2+} also binds to specific Ca^{2+}-binding proteins (CBPs) such as calmodulin (CaM) which then activate multiple target proteins in the cell including enzymes, membrane transport pumps, and ion channels. CaM interactions are involved in a multitude of cellular processes including, but not limited to, gene regulation, DNA synthesis, cell cycle progression, mitosis, cytokinesis, cytoskeletal organization, muscle contraction, signal transduction, ion homeostasis, exocytosis, and metabolic regulation (Celio, M.R. et al. (1996) Guidebook to Calcium-binding Proteins, Oxford University Press, Oxford, UK, pp. 15-20). Some Ca^{2+} binding proteins are characterized by the presence of one or more EF-hand Ca^{2+} binding motifs, which are comprised of 12 amino acids flanked by α-helices (Celio, supra). The regulation of CBPs has implications for the control of a variety of disorders. Calcineurin, a CaM-regulated protein phosphatase, is a target for inhibition by the immunosuppressive agents cyclosporin and FK506. This indicates the importance of calcineurin and CaM in the immune response and immune disorders (Schwaninger M. et al. (1993) J. Biol Chem. 268:23111-23115). The level of CaM is increased several-fold in tumors and tumor-derived cell lines for various types of cancer (Rasmussen, C.D. and Means, A.R. (1989) Trends in Neuroscience 12:433-438).

The annexins are a family of calcium-binding proteins that associate with the cell membrane (Towle, C.A. and Treadwell, B.V. (1992) J. Biol. Chem. 267:5416-23). Annexins reversibly bind to negatively charged phospholipids (phosphatidylcholine and phosphatidylserine) in a calcium dependent manner. Annexins participate in various processes pertaining to signal transduction at the plasma membrane, including membrane-cytoskeleton interactions, phospholipase inhibition, anticoagulation, and membrane fusion. Annexins contain four to eight repeated segments of about 60 residues. Each repeat folds into five alpha helices wound into a right-handed superhelix.

Signaling Complex Protein Domains

PDZ domains were named for three proteins in which this domain was initially discovered. These proteins include PSD-95 (postsynaptic density 95), Dlg (Drosophila lethal(1)discs large-1), and ZO-1 (zonula occludens-1). These proteins play important roles in neuronal synaptic transmission, tumor suppression, and cell junction formation, respectively. Since the discovery of these proteins, over sixty additional PDZ-containing proteins have been identified in diverse prokaryotic and eukaryotic organisms. This domain has been implicated in receptor and ion channel clustering and in the targeting of multiprotein signaling complexes to specialized functional regions of the cytosolic face of the plasma membrane. (For review of PDZ domain-containing proteins, see Ponting, C. P. et al. (1997) Bioessays 19:469-479.) A large proportion of PDZ domains are found in the eukaryotic MAGUK (membrane-associated guanylate kinase) protein family, members of which bind to the

intracellular domains of receptors and channels. However, PDZ domains are also found in diverse membrane-localized proteins such as protein tyrosine phosphatases, serine/threonine kinases, G-protein cofactors, and synapse-associated proteins such as syntrophins and neuronal nitric oxide synthase (nNOS). Generally, about one to three PDZ domains are found in a given protein, although up to nine PDZ domains have been identified in a single protein. The glutamate receptor interacting protein (GRIP) contains seven PDZ domains. GRIP is an adaptor that links certain glutamate receptors to other proteins and may be responsible for the clustering of these receptors at excitatory synapses in the brain (Dong, H. et al. (1997) Nature 386:279-284).

The SH3 domain is defined by homology to a region of the proto-oncogene c-Src, a cytoplasmic protein tyrosine kinase. SH3 is a small domain of 50 to 60 amino acids that interacts with proline-rich ligands. SH3 domains are found in a variety of eukaryotic proteins involved in signal transduction, cell polarization, and membrane-cytoskeleton interactions. In some cases, SH3 domain-containing proteins interact directly with receptor tyrosine kinases. For example, the SLAP-130 protein is a substrate of the T-cell receptor (TCR) stimulated protein kinase. SLAP-130 interacts via its SH3 domain with the protein SLP-76 to affect the TCR-induced expression of interleukin-2 (Musci, M.A. et al. (1997) J. Biol. Chem. 272:11674-11677). Another recently identified SH3 domain protein is macrophage actin-associated tyrosine-phosphorylated protein (MAYP) which is phosphorylated during the response of macrophages to colony stimulating factor-1 (CSF-1) and is likely to play a role in regulating the CSF-1-induced reorganization of the actin cytoskeleton (Yeung, Y.-G. et al. (1998) J. Biol. Chem. 273:30638-30642). The structure of SH3 is characterized by two antiparallel beta sheets packed against each other at right angles. This packing forms a hydrophobic pocket lined with residues that are highly conserved between different SH3 domains. This pocket makes critical hydrophobic contacts with proline residues in the ligand (Feng, S. et al. (1994) Science 266: 1241-47). Endophilin is an SH3 domain-containing protein implicated in synaptic vesicle endocytosis. (Micheva, K.D. (1997) 272:27239-27245).

A novel domain, called the WW domain, resembles the SH3 domain in its ability to bind proline-rich ligands. This domain was originally discovered in dystrophin, a cytoskeletal protein with direct involvement in Duchenne muscular dystrophy (Bork, P. and Sudol, M. (1994) Trends Biochem. Sci. 19:531-533). WW domains have since been discovered in a variety of intracellular signaling molecules involved in development, cell differentiation, and cell proliferation. The structure of the WW domain is composed of beta strands grouped around four conserved aromatic residues, generally tryptophan.

Like SH3, the SH2 domain is defined by homology to a region of c-Src. SH2 domains interact directly with phospho-tyrosine residues, thus providing an immediate mechanism for the regulation and transduction of receptor tyrosine kinase-mediated signaling pathways. For example, as

many as ten distinct SH2 domains are capable of binding to phosphorylated tyrosine residues in the activated PDGF receptor, thereby providing a highly coordinated and finely tuned response to ligand-mediated receptor activation. (Reviewed in Schaffhausen, B. (1995) Biochem. Biophys. Acta. 1242:61-75.)

Homer is a neuronal immediate early gene that is enriched at excitatory synapses (Xiao, B. et al. (1998) Neuron 21:707-716). Homer proteins form multivalent complexes that bind proline-rich motifs in group 1 metabotropic glutamate receptors and inositol triphosphate receptors, thereby coupling these receptors in a signaling complex (Tu, J.C. (1999) Neuron 23:583-592).

The pleckstrin homology (PH) domain was originally identified in pleckstrin, the predominant substrate for protein kinase C in platelets. Since its discovery, this domain has been identified in over 90 proteins involved in intracellular signaling or cytoskeletal organization. Proteins containing the pleckstrin homology domain include a variety of kinases, phospholipase-C isoforms, guanine nucleotide release factors, and GTPase activating proteins. For example, members of the FGD1 family contain both Rho-guanine nucleotide exchange factor (GEF) and PH domains, as well as a FYVE zinc finger domain. FGD1 is the gene responsible for faciogenital dysplasia, an inherited skeletal dysplasia (Pasteris, N.G. and Gorski, J.L. (1999) Genomics 60:57-66). Many PH domain proteins function in association with the plasma membrane, and this association appears to be mediated by the PH domain itself. PH domains share a common structure composed of two antiparallel beta sheets flanked by an amphipathic alpha helix. Variable loops connecting the component beta strands generally occur within a positively charged environment and may function as ligand binding sites (Lemmon, M. A. et al. (1996) Cell 85:621-624.). n-Chimaerin is a GAP involved in the formation of lamellipodia and filopodia in neuroblastoma cells. (Kozma, R. et al. (1996) Mol. Cell Biol. 16:5069-5080.)

Ankyrin (ANK) repeats mediate protein-protein interactions associated with diverse intracellular signaling functions. For example, ANK repeats are found in proteins involved in cell proliferation such as kinases, kinase inhibitors, tumor suppressors, and cell cycle control proteins. (See, for example, Kalus, W. et al. (1997) FEBS Lett. 401:127-132; Ferrante, A. W. et al. (1995) Proc. Natl. Acad. Sci. USA 92:1911-1915.) These proteins generally contain multiple ANK repeats, each composed of about 33 amino acids. Myotrophin is an ANK repeat protein that plays a key role in the development of cardiac hypertrophy, a contributing factor to many heart diseases. Structural studies show that the myotrophin ANK repeats, like other ANK repeats, each form a helix-turn-helix core preceded by a protruding "tip." These tips are of variable sequence and may play a role in protein-protein interactions. The helix-turn-helix region of the ANK repeats stack on top of one another and are stabilized by hydrophobic interactions (Yang, Y. et al. (1998) Structure 6:619-626).

The tetratrico peptide repeat (TPR) is a 34 amino acid repeated motif found in organisms

from bacteria to humans. TPRs are predicted to form ampipathic helices, and appear to mediate protein-protein interactions. TPR domains are found in CDC16, CDC23, and CDC27, members the the anaphase promoting complex which targets proteins for degradation at the onset of anaphase. Other processes involving TPR proteins include cell cycle control, transcription repression, stress response, and protein kinase inhibition. (Lamb, J.R. et al. (1995) Trends Biochem. Sci. 20:257-259.)

The armadillo/beta-catenin repeat is a 42 amino acid motif which forms a superhelix of alpha helices when tandemly repeated. The structure of the armadillo repeat region from beta-catenin revealed a shallow groove of positive charge on one face of the superhelix, which is a potential binding surface. The armadillo repeats of beta-catenin, plakoglobin, and p120^{cas} bind the cytoplasmic domains of cadherins. Beta-catenin/cadherin complexes are targets of regulatory signals that govern cell adhesion and mobility. (Huber, A.H. et al. (1997) Cell 90:871-882.)

The discovery of new intracellular signaling proteins and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of cell proliferative, autoimmune/inflammatory, reproductive, and developmental disorders.

SUMMARY OF THE INVENTION

The invention features purified polypeptides, intracellular signaling molecules, referred to collectively as "INTRA" and individually as "INTRA-1," "INTRA-2," "INTRA-3," "INTRA-4," "INTRA-5," "INTRA-6," "INTRA-7," "INTRA-8," "INTRA-9," "INTRA-10," "INTRA-11," "INTRA-12," "INTRA-13," "INTRA-14," "INTRA-15," "INTRA-16," "INTRA-17," "INTRA-18," "INTRA-19," "INTRA-20," "INTRA-21," "INTRA-22," "INTRA-23," "INTRA-24," "INTRA-25," "INTRA-26." "INTRA-27," "INTRA-28," "INTRA-29," "INTRA-30," "INTRA-31," "INTRA-32," "INTRA-33," "INTRA-34," "INTRA-35," "INTRA-36," "INTRA-37," "INTRA-38," "INTRA-39," "INTRA-40," "INTRA-41," "INTRA-42," "INTRA-43," "INTRA-44," "INTRA-45," "INTRA-46," "INTRA-47," "INTRA-48," "INTRA-49," "INTRA-50," "INTRA-51," and "INTRA-52." In one aspect, the invention provides an isolated polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. In one alternative, the invention provides an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1-52.

The invention further provides an isolated polynucleotide encoding a polypeptide comprising

an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. In one alternative, the polynucleotide encodes a polypeptide selected from the group consisting of SEQ ID NO:1-52. In another alternative, the polynucleotide is selected from the group consisting of SEQ ID NO:53-104.

Additionally, the invention provides a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. In one alternative, the invention provides a cell transformed with the recombinant polynucleotide. In another alternative, the invention provides a transgenic organism comprising the recombinant polynucleotide.

The invention also provides a method for producing a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. The method comprises a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding the polypeptide, and b) recovering the polypeptide so expressed.

Additionally, the invention provides an isolated antibody which specifically binds to a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52.

The invention further provides an isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). In one alternative, the polynucleotide comprises at least 60 contiguous nucleotides.

Additionally, the invention provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). The method comprises a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and b) detecting the presence or absence of said hybridization complex, and optionally, if present, the amount thereof. In one alternative, the probe comprises at least 60 contiguous nucleotides.

The invention further provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). The method comprises a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

The invention further provides a pharmaceutical composition comprising an effective amount of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence

selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and a pharmaceutically acceptable excipient. In one embodiment, the pharmaceutical composition comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. The invention additionally provides a method of treating a disease or condition associated with decreased expression of functional INTRA, comprising administering to a patient in need of such treatment the pharmaceutical composition.

The invention also provides a method for screening a compound for effectiveness as an agonist of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting agonist activity in the sample. In one alternative, the invention provides a pharmaceutical composition comprising an agonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with decreased expression of functional INTRA, comprising administering to a patient in need of such treatment the pharmaceutical composition.

Additionally, the invention provides a method for screening a compound for effectiveness as an antagonist of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting antagonist activity in the sample. In one alternative, the invention provides a pharmaceutical composition comprising an antagonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with overexpression of functional INTRA, comprising administering to a patient in need of such treatment the pharmaceutical composition.

The invention further provides a method of screening for a compound that specifically binds to a polypeptide comprising an amino acid sequence selected from the group consisting of a) an

amino acid sequence selected from the group consisting of SEQ ID NO:1-52. b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. The method comprises a) combining the polypeptide with at least one test compound under suitable conditions, and b) detecting binding of the polypeptide to the test compound, thereby identifying a compound that specifically binds to the polypeptide.

The invention further provides a method of screening for a compound that modulates the activity of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. The method comprises a) combining the polypeptide with at least one test compound under conditions permissive for the activity of the polypeptide, b) assessing the activity of the polypeptide in the presence of the test compound, and c) comparing the activity of the polypeptide in the presence of the test compound with the activity of the polypeptide in the absence of the test compound, wherein a change in the activity of the polypeptide in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide.

The invention further provides a method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence selected from the group consisting of SEQ ID NO:53-104, the method comprising a) exposing a sample comprising the target polynucleotide to a compound, and b) detecting altered expression of the target polynucleotide.

BRIEF DESCRIPTION OF THE TABLES

Table 1 shows polypeptide and nucleotide sequence identification numbers (SEQ ID NOs), clone identification numbers (clone IDs), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding INTRA.

Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods, algorithms, and searchable databases used for analysis of INTRA.

Table 3 shows selected fragments of each nucleic acid sequence; the tissue-specific expression patterns of each nucleic acid sequence as determined by northern analysis; diseases,

disorders, or conditions associated with these tissues; and the vector into which each cDNA was cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which cDNA clones encoding INTRA were isolated.

Table 5 shows the tools, programs, and algorithms used to analyze the polynucleotides and polypeptides of the invention, along with applicable descriptions, references, and threshold parameters.

DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

DEFINITIONS

"INTRA" refers to the amino acid sequences of substantially purified INTRA obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and human, and from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which intensifies or mimics the biological activity of INTRA. Agonists may include proteins, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of INTRA either by directly interacting with INTRA or by acting on components of the biological pathway in which INTRA participates.

An "allelic variant" is an alternative form of the gene encoding INTRA. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. A gene may have none, one, or many allelic variants of its naturally occurring form. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

"Altered" nucleic acid sequences encoding INTRA include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polypeptide the same as INTRA or a polypeptide with at least one functional characteristic of INTRA. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding INTRA, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding INTRA. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent INTRA. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of INTRA is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, and positively charged amino acids may include lysine and arginine. Amino acids with uncharged polar side chains having similar hydrophilicity values may include: asparagine and glutamine; and serine and threonine. Amino acids with uncharged side chains having similar hydrophilicity values may include: leucine, isoleucine, and valine; glycine and alanine; and phenylalanine and tyrosine.

The terms "amino acid" and "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited to refer to a sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

The term "antagonist" refers to a molecule which inhibits or attenuates the biological activity of INTRA. Antagonists may include proteins such as antibodies, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of INTRA either by directly interacting with INTRA or by acting on components of the biological pathway in which

INTRA participates.

The term "antibody" refers to intact immunoglobulin molecules as well as to fragments thereof, such as Fab, $F(ab')_2$, and Fv fragments, which are capable of binding an epitopic determinant. Antibodies that bind INTRA polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

The term "antigenic determinant" refers to that region of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (particular regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition capable of base-pairing with the "sense" (coding) strand of a specific nucleic acid sequence. Antisense compositions may include DNA; RNA; peptide nucleic acid (PNA); oligonucleotides having modified backbone linkages such as phosphorothioates, methylphosphonates, or benzylphosphonates; oligonucleotides having modified sugar groups such as 2'-methoxyethyl sugars or 2'-methoxyethoxy sugars; or oligonucleotides having modified bases such as 5-methyl cytosine, 2'-deoxyuracil, or 7-deaza-2'-deoxyguanosine. Antisense molecules may be produced by any method including chemical synthesis or transcription. Once introduced into a cell, the complementary antisense molecule base-pairs with a naturally occurring nucleic acid sequence produced by the cell to form duplexes which block either transcription or translation. The designation "negative" or "minus" can refer to the antisense strand, and the designation "positive" or "plus" can refer to the sense strand of a reference DNA molecule.

The term "biologically active" refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" or "immunogenic" refers to the capability of the natural, recombinant, or synthetic INTRA, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

"Complementary" describes the relationship between two single-stranded nucleic acid sequences that anneal by base-pairing. For example, 5'-AGT-3' pairs with its complement, 3'-TCA-5'.

A "composition comprising a given polynucleotide sequence" and a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding INTRA or fragments of INTRA may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been subjected to repeated DNA sequence analysis to resolve uncalled bases, extended using the XL-PCR kit (PE Biosystems, Foster City CA) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from one or more overlapping cDNA, EST, or genomic DNA fragments using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI) or Phrap (University of Washington, Seattle WA). Some sequences have been both extended and assembled to produce the consensus sequence.

"Conservative amino acid substitutions" are those substitutions that are predicted to least interfere with the properties of the original protein, i.e., the structure and especially the function of the protein is conserved and not significantly changed by such substitutions. The table below shows amino acids which may be substituted for an original amino acid in a protein and which are regarded as conservative amino acid substitutions.

Original Residue	Conservative Substitution
Ala	Gly, Ser
Arg	His, Lys
Asn	Asp, Gln, His
Asp	Asn, Glu
Cys	Ala, Ser
Gln	Asn, Glu, His
Glu	Asp, Gln, His
Gly	Ala
His	Asn, Arg, Gln, Glu
Ile	Leu, Val
Leu	Ile, Val
Lys	Arg, Gln, Glu
Met	Leu, Ile
Phe	His, Met, Leu, Trp, Tyr
Ser	Cys, Thr
Thr	Ser, Val
Trp	Phe, Tyr
Tyr	His, Phe, Trp
Val	Ile, Leu, Thr

Conservative amino acid substitutions generally maintain (a) the structure of the polypeptide

backbone in the area of the substitution. for example, as a beta sheet or alpha helical conformation. (b) the charge or hydrophobicity of the molecule at the site of the substitution, and/or (c) the bulk of the side chain.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to a chemically modified polynucleotide or polypeptide. Chemical modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, hydroxyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

A "detectable label" refers to a reporter molecule or enzyme that is capable of generating a measurable signal and is covalently or noncovalently joined to a polynucleotide or polypeptide.

A "fragment" is a unique portion of INTRA or the polynucleotide encoding INTRA which is identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up to the entire length of the defined sequence, minus one nucleotide/amino acid residue. For example, a fragment may comprise from 5 to 1000 contiguous nucleotides or amino acid residues. A fragment used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least 5, 10, 15, 16, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous nucleotides or amino acid residues in length. Fragments may be preferentially selected from certain regions of a molecule. For example, a polypeptide fragment may comprise a certain length of contiguous amino acids selected from the first 250 or 500 amino acids (or first 25% or 50% of a polypeptide) as shown in a certain defined sequence. Clearly these lengths are exemplary, and any length that is supported by the specification, including the Sequence Listing, tables, and figures, may be encompassed by the present embodiments.

A fragment of SEQ ID NO:53-104 comprises a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:53-104, for example, as distinct from any other sequence in the genome from which the fragment was obtained. A fragment of SEQ ID NO:53-104 is useful, for example, in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:53-104 from related polynucleotide sequences. The precise length of a fragment of SEQ ID NO:53-104 and the region of SEQ ID NO:53-104 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A fragment of SEQ ID NO:1-52 is encoded by a fragment of SEQ ID NO:53-104. A fragment of SEQ ID NO:1-52 comprises a region of unique amino acid sequence that specifically

identifies SEQ ID NO:1-52. For example, a fragment of SEQ ID NO:1-52 is useful as an immunogenic peptide for the development of antibodies that specifically recognize SEQ ID NO:1-52. The precise length of a fragment of SEQ ID NO:1-52 and the region of SEQ ID NO:1-52 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A "full-length" polynucleotide sequence is one containing at least a translation initiation codon (e.g., methionine) followed by an open reading frame and a translation termination codon. A "full-length" polynucleotide sequence encodes a "full-length" polypeptide sequence.

"Homology" refers to sequence similarity or, interchangeably, sequence identity, between two or more polynucleotide sequences or two or more polypeptide sequences.

The terms "percent identity" and "% identity," as applied to polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in the sequences being compared in order to optimize alignment between two sequences, and therefore achieve a more meaningful comparison of the two sequences.

Percent identity between polynucleotide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program. This program is part of the LASERGENE software package, a suite of molecular biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in Higgins, D.G. and P.M. Sharp (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191. For pairwise alignments of polynucleotide sequences, the default parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted" residue weight table is selected as the default. Percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polynucleotide sequences.

Alternatively, a suite of commonly used and freely available sequence comparison algorithms is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, MD, and on the Internet at http://www.ncbi.nlm.nih.gov/BLAST/. The BLAST software suite includes various sequence analysis programs including "blastn," that is used to align a known polynucleotide sequence with other polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2 Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at http://www.ncbi.nlm.nih.gov/gorf/bl2.html. The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST programs are commonly used with gap and other parameters set to default settings. For example, to

compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.12 (April-21-2000) set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Reward for match: 1

Penalty for mismatch: -2

Open Gap: 5 and Extension Gap: 2 penalties

Gap x drop-off: 50

Expect: 10

Word Size: 11

Filter: on

Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous nucleotides. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures, or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

Nucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences that all encode substantially the same protein.

The phrases "percent identity" and "% identity," as applied to polypeptide sequences, refer to the percentage of residue matches between at least two polypeptide sequences aligned using a standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some alignment methods take into account conservative amino acid substitutions. Such conservative substitutions, explained in more detail above, generally preserve the charge and hydrophobicity at the site of substitution, thus preserving the structure (and therefore function) of the polypeptide.

Percent identity between polypeptide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program (described and referenced above). For pairwise alignments of polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap penalty=3, window=5, and "diagonals saved"=5. The PAM250 matrix is selected as the default residue weight table. As with polynucleotide alignments, the percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polypeptide sequence pairs.

Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise

comparison of two polypeptide sequences, one may use the "BLAST 2 Sequences" tool Version 2.0.12 (Apr-21-2000) with blastp set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62
Open Gap: 11 and Extension Gap: 1 penalties
Gap x drop-off: 50
Expect: 10
Word Size: 3
Filter: on

Percent identity may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for chromosome replication, segregation and maintenance.

The term "humanized antibody" refers to an antibody molecule in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to the process by which a polynucleotide strand anneals with a complementary strand through base pairing under defined hybridization conditions. Specific hybridization is an indication that two nucleic acid sequences share a high degree of complementarity. Specific hybridization complexes form under permissive annealing conditions and remain hybridized after the "washing" step(s). The washing step(s) is particularly important in determining the stringency of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e., binding between pairs of nucleic acid strands that are not perfectly matched. Permissive conditions for annealing of nucleic acid sequences are routinely determinable by one of ordinary skill in the art and may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency, and therefore hybridization specificity. Permissive annealing conditions occur, for example, at 68°C in the presence of about 6 x SSC, about 1% (w/v) SDS, and about 100 μg/ml sheared, denatured salmon sperm DNA.

Generally, stringency of hybridization is expressed, in part, with reference to the temperature

under which the wash step is carried out. Such wash temperatures are typically selected to be about 5°C to 20°C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. An equation for calculating T_m and conditions for nucleic acid hybridization are well known and can be found in Sambrook, J. et al., 1989, Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; specifically see volume 2, chapter 9.

High stringency conditions for hybridization between polynucleotides of the present invention include wash conditions of 68°C in the presence of about 0.2 x SSC and about 0.1% SDS, for 1 hour. Alternatively, temperatures of about 65°C, 60°C, 55°C, or 42°C may be used. SSC concentration may be varied from about 0.1 to 2 x SSC, with SDS being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance, sheared and denatured salmon sperm DNA at about 100-200 μg/ml. Organic solvent, such as formamide at a concentration of about 35-50% v/v, may also be used under particular circumstances, such as for RNA:DNA hybridizations. Useful variations on these wash conditions will be readily apparent to those of ordinary skill in the art. Hybridization, particularly under high stringency conditions, may be suggestive of evolutionary similarity between the nucleotides. Such similarity is strongly indicative of a similar role for the nucleotides and their encoded polypeptides.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g., C_0t or R_0t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

The words "insertion" and "addition" refer to changes in an amino acid or nucleotide sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

An "immunogenic fragment" is a polypeptide or oligopeptide fragment of INTRA which is capable of eliciting an immune response when introduced into a living organism, for example, a mammal. The term "immunogenic fragment" also includes any polypeptide or oligopeptide fragment of INTRA which is useful in any of the antibody production methods disclosed herein or known in the art.

The term "microarray" refers to an arrangement of a plurality of polynucleotides, polypeptides, or other chemical compounds on a substrate.

The terms "element" and "array element" refer to a polynucleotide, polypeptide, or other chemical compound having a unique and defined position on a microarray.

The term "modulate" refers to a change in the activity of INTRA. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of INTRA.

The phrases "nucleic acid" and "nucleic acid sequence" refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material.

"Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a functional relationship with a second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Operably linked DNA sequences may be in close proximity or contiguous and, where necessary to join two protein coding regions, in the same reading frame.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

"Post-translational modification" of an INTRA may involve lipidation, glycosylation, phosphorylation, acetylation, racemization, proteolytic cleavage, and other modifications known in the art. These processes may occur synthetically or biochemically. Biochemical modifications will vary by cell type depending on the enzymatic milieu of INTRA.

"Probe" refers to nucleic acid sequences encoding INTRA, their complements, or fragments thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oligonucleotides or polynucleotides attached to a detectable label or reporter molecule. Typical labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes.

"Primers" are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target polynucleotide by complementary base-pairing. The primer may then be extended along the target DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification (and identification) of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR).

Probes and primers as used in the present invention typically comprise at least 15 contiguous nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also

be employed, such as probes and primers that comprise at least 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers may be considerably longer than these examples, and it is understood that any length supported by the specification, including the tables, figures, and Sequence Listing, may be used.

Methods for preparing and using probes and primers are described in the references, for example Sambrook, J. et al., 1989, Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; Ausubel, F.M. et al.,1987, Current Protocols in Molecular Biology, Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis, M. et al., 1990, PCR Protocols, A Guide to Methods and Applications, Academic Press, San Diego CA. PCR primer pairs can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge MA).

Oligonucleotides for use as primers are selected using software known in the art for such purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to 100 nucleotides each, and for the analysis of oligonucleotides and larger polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection programs have incorporated additional features for expanded capabilities. For example, the PrimOU primer selection program (available to the public from the Genome Center at University of Texas South West Medical Center, Dallas TX) is capable of choosing specific primers from megabase sequences and is thus useful for designing primers on a genome-wide scope. The Primer3 primer selection program (available to the public from the Whitehead Institute/MIT Center for Genome Research, Cambridge MA) allows the user to input a "mispriming library," in which sequences to avoid as primer binding sites are user-specified. Primer3 is useful, in particular, for the selection of oligonucleotides for microarrays. (The source code for the latter two primer selection programs may also be obtained from their respective sources and modified to meet the user's specific needs.) The PrimeGen program (available to the public from the UK Human Genome Mapping Project Resource Centre, Cambridge UK) designs primers based on multiple sequence alignments, thereby allowing selection of primers that hybridize to either the most conserved or least conserved regions of aligned nucleic acid sequences. Hence, this program is useful for identification of both unique and conserved oligonucleotides and polynucleotide fragments. The oligonucleotides and polynucleotide fragments identified by any of the above selection methods are useful in hybridization technologies, for example, as PCR or sequencing primers, microarray elements, or specific probes to identify fully or partially complementary polynucleotides in a sample of nucleic acids. Methods of oligonucleotide selection are not limited to those described above.

A "recombinant nucleic acid" is a sequence that is not naturally occurring or has a sequence

that is made by an artificial combination of two or more otherwise separated segments of sequence. This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques such as those described in Sambrook, supra. The term recombinant includes nucleic acids that have been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a recombinant nucleic acid may include a nucleic acid sequence operably linked to a promoter sequence. Such a recombinant nucleic acid may be part of a vector that is used, for example, to transform a cell.

Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a vaccinia virus, that could be use to vaccinate a mammal wherein the recombinant nucleic acid is expressed, inducing a protective immunological response in the mammal.

A "regulatory element" refers to a nucleic acid sequence usually derived from untranslated regions of a gene and includes enhancers, promoters, introns, and 5' and 3' untranslated regions (UTRs). Regulatory elements interact with host or viral proteins which control transcription, translation, or RNA stability.

"Reporter molecules" are chemical or biochemical moieties used for labeling a nucleic acid, amino acid, or antibody. Reporter molecules include radionuclides; enzymes; fluorescent, chemiluminescent, or chromogenic agents; substrates; cofactors; inhibitors; magnetic particles; and other moieties known in the art.

An "RNA equivalent," in reference to a DNA sequence, is composed of the same linear sequence of nucleotides as the reference DNA sequence with the exception that all occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

The term "sample" is used in its broadest sense. A sample suspected of containing nucleic acids encoding INTRA, or fragments thereof, or INTRA itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" and "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or synthetic binding composition. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide comprising the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

The term "substantially purified" refers to nucleic acid or amino acid sequences that are

removed from their natural environment and are isolated or separated, and are at least 60% free, preferably at least 75% free, and most preferably at least 90% free from other components with which they are naturally associated.

A "substitution" refers to the replacement of one or more amino acid residues or nucleotides by different amino acid residues or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

A "transcript image" refers to the collective pattern of gene expression by a particular cell type or tissue under given conditions at a given time.

"Transformation" describes a process by which exogenous DNA is introduced into a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, bacteriophage or viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

A "transgenic organism," as used herein, is any organism, including but not limited to animals and plants, in which one or more of the cells of the organism contains heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or in vitro fertilization, but rather is directed to the introduction of a recombinant DNA molecule. The transgenic organisms contemplated in accordance with the present invention include bacteria, cyanobacteria, fungi, plants, and animals. The isolated DNA of the present invention can be introduced into the host by methods known in the art, for example infection, transfection, transformation or transconjugation. Techniques for transferring the DNA of the present invention into such organisms are widely known and provided in references such as Sambrook et al. (1989), supra.

A "variant" of a particular nucleic acid sequence is defined as a nucleic acid sequence having at least 40% sequence identity to the particular nucleic acid sequence over a certain length of one of

the nucleic acid sequences using blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of nucleic acids may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98% or greater sequence identity over a certain defined length. A variant may be described as, for example, an "allelic" (as defined above), "splice," "species," or "polymorphic" variant. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternative splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or lack domains that are present in the reference molecule. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one nucleotide base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

A "variant" of a particular polypeptide sequence is defined as a polypeptide sequence having at least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98% or greater sequence identity over a certain defined length of one of the polypeptides.

THE INVENTION

The invention is based on the discovery of new human intracellular signaling molecules (INTRA), the polynucleotides encoding INTRA, and the use of these compositions for the diagnosis, treatment, or prevention of cell proliferative, autoimmune/inflammatory, neurological, gastrointestinal, reproductive, and developmental disorders.

Table 1 lists the Incyte clones used to assemble full length nucleotide sequences encoding INTRA. Columns 1 and 2 show the sequence identification numbers (SEQ ID NOs) of the polypeptide and nucleotide sequences, respectively. Column 3 shows the clone IDs of the Incyte clones in which nucleic acids encoding each INTRA were identified, and column 4 shows the cDNA libraries from which these clones were isolated. Column 5 shows Incyte clones and their corresponding cDNA libraries. Clones for which cDNA libraries are not indicated were derived from pooled cDNA libraries. In some cases, GenBank sequence identifiers are also shown in column 5. The Incyte clones and GenBank cDNA sequences, where indicated, in column 5 were used to assemble the consensus nucleotide sequence of each INTRA and are useful as fragments in

hybridization technologies.

The columns of Table 2 show various properties of each of the polypeptides of the invention: column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues in each polypeptide; column 3 shows potential phosphorylation sites; column 4 shows potential glycosylation sites; column 5 shows the amino acid residues comprising signature sequences and motifs; column 6 shows homologous sequences as identified by BLAST analysis along with relevant citations, all of which are expressly incorporated by reference herein in their entirety; and column 7 shows analytical methods and in some cases, searchable databases to which the analytical methods were applied. The methods of column 7 were used to characterize each polypeptide through sequence homology and protein motifs.

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding INTRA. The first column of Table 3 lists the nucleotide SEQ ID NOs. Column 2 lists fragments of the nucleotide sequences of column 1. These fragments are useful, for example, in hybridization or amplification technologies to identify SEQ ID NO:53-104 and to distinguish between SEQ ID NO:53-104 and related polynucleotide sequences. The polypeptides encoded by these fragments are useful, for example, as immunogenic peptides. Column 3 lists tissue categories which express INTRA as a fraction of total tissues expressing INTRA. Column 4 lists diseases, disorders, or conditions associated with those tissues expressing INTRA as a fraction of total tissues expressing INTRA. Column 5 lists the vectors used to subclone each cDNA library. Of particular interest is the expression of SEQ ID NO:88 and SEQ ID NO:94 in reproductive tissues, of SEQ ID NO:99, SEQ ID NO:100, and SEQ ID NO:103 in hematopoietic/immune tissues, and of SEQ ID NO:96 in cardiovascular tissues.

The columns of Table 4 show descriptions of the tissues used to construct the cDNA libraries from which cDNA clones encoding INTRA were isolated. Column 1 references the nucleotide SEQ ID NOs, column 2 shows the cDNA libraries from which these clones were isolated, and column 3 shows the tissue origins and other descriptive information relevant to the cDNA libraries in column 2.

SEQ ID NO:58 maps to chromosome 7 within the interval from 84.40 to 90.30 centiMorgans. This interval also contains an EST with high similarity to thyroid disease hypothetical autoantigen. SEQ ID NO:67 maps to chromosome 16 within the interval from 119.20 centiMorgans to q-terminus. This interval also contains the paraplegin gene, mutations in which cause spastic paraplegia and OXPHOS impairment. SEQ ID NO:70 maps to chromosome 11 within the interval from 59.50 to 62.50 centiMorgans. SEQ ID NO:71 maps to chromosome 7 within the interval from 138.0 to 145.8 centiMorgans. SEQ ID NO:73 maps to chromosome 12 within the interval from 76.5 to 84.2 centiMorgans. SEQ ID NO:77 maps to chromosome 7 within the interval from 4.8 to 10.6 centiMorgans and to chromosome 4 within the interval from 56.7 to 60.5 centiMorgans. The interval

on chromosome 7 from from 4.8 to 10.6 centiMorgans also contains a gene associated with cell proliferation. The interval on chromosome 4 from 56.7 to 60.5 centiMorgans also contains a gene associated with cell proliferation. SEQ ID NO:79 maps to chromosome 15 within the interval from 32.2 to 47.1 centiMorgans. This interval also contains a gene associated with cell proliferation. SEQ ID NO:80 maps to chromosome 20 within the interval from 50.2 to 53.6 centiMorgans. This interval also contains a gene associated with cell differentiation. SEQ ID NO:84 maps to chromosome 3 within the interval from 142.2 to 148.7 centiMorgans. SEQ ID NO:87 maps to chromosome 5 within the interval from 141.4 to 147.1 centiMorgans. SEQ ID NO:91 maps to chromosome 12 within the interval from 62.7 to 67.3 centiMorgans. SEQ ID NO:95 maps to chromosome 15 within the interval from 45.5 to 58.8 centiMorgans. SEQ ID NO:97 maps to the X chromosome within the interval from 112.8 to 139.4 centiMorgans.

The invention also encompasses INTRA variants. A preferred INTRA variant is one which has at least about 80%, or alternatively at least about 90%, or even at least about 95% amino acid sequence identity to the INTRA amino acid sequence, and which contains at least one functional or structural characteristic of INTRA.

The invention also encompasses polynucleotides which encode INTRA. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:53-104, which encodes INTRA. The polynucleotide sequences of SEQ ID NO:53-104, as presented in the Sequence Listing, embrace the equivalent RNA sequences, wherein occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

The invention also encompasses a variant of a polynucleotide sequence encoding INTRA. In particular, such a variant polynucleotide sequence will have at least about 80%, or alternatively at least about 90%, or even at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding INTRA. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:53-104 which has at least about 80%, or alternatively at least about 90%, or even at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:53-104. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of INTRA.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding INTRA, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These

combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring INTRA, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode INTRA and its variants are generally capable of hybridizing to the nucleotide sequence of the naturally occurring INTRA under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding INTRA or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding INTRA and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode INTRA and INTRA derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding INTRA or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:53-104 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) Methods Enzymol. 152:399-407; Kimmel, A.R. (1987) Methods Enzymol. 152:507-511.) Hybridization conditions, including annealing and wash conditions, are described in "Definitions."

Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (PE Biosystems, Foster City CA), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV), PTC200 thermal cycler (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cycler (PE Biosystems). Sequencing is then carried out using either the ABI 373 or 377 DNA sequencing system (PE Biosystems), the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting

sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding INTRA may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) PCR Methods Applic. 2:318-322.) Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) Nucleic Acids Res. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et al. (1991) PCR Methods Applic. 1:111-119.) In this method, multiple restriction enzyme digestions and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) Nucleic Acids Res. 19:3055-3060). Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 Primer Analysis software (National Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

When screening for full-length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate

software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, PE Biosystems), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode INTRA may be cloned in recombinant DNA molecules that direct expression of INTRA, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express INTRA.

The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter INTRA-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

The nucleotides of the present invention may be subjected to DNA shuffling techniques such as MOLECULARBREEDING (Maxygen Inc., Santa Clara CA; described in U.S. Patent Number 5,837,458; Chang, C.-C. et al. (1999) Nat. Biotechnol. 17:793-797; Christians, F.C. et al. (1999) Nat. Biotechnol. 17:259-264; and Crameri, A. et al. (1996) Nat. Biotechnol. 14:315-319) to alter or improve the biological properties of INTRA, such as its biological or enzymatic activity or its ability to bind to other molecules or compounds. DNA shuffling is a process by which a library of gene variants is produced using PCR-mediated recombination of gene fragments. The library is then subjected to selection or screening procedures that identify those gene variants with the desired properties. These preferred variants may then be pooled and further subjected to recursive rounds of DNA shuffling and selection/screening. Thus, genetic diversity is created through "artificial" breeding and rapid molecular evolution. For example, fragments of a single gene containing random point mutations may be recombined, screened, and then reshuffled until the desired properties are optimized. Alternatively, fragments of a given gene may be recombined with fragments of homologous genes in the same gene family, either from the same or different species, thereby maximizing the genetic diversity of multiple naturally occurring genes in a directed and controllable manner.

In another embodiment, sequences encoding INTRA may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucleic Acids Symp. Ser. 7:215-223; and Horn, T. et al. (1980) Nucleic Acids Symp. Ser. 7:225-232.)

Alternatively, INTRA itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solution-phase or solid-phase techniques. (See, e.g., Creighton, T. (1984) Proteins. Structures and Molecular Properties, WH Freeman, New York NY, pp. 55-60; and Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using the ABI 431A peptide synthesizer (PE Biosystems). Additionally, the amino acid sequence of INTRA, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide or a polypeptide having a sequence of a naturally occurring polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, supra, pp. 28-53.)

In order to express a biologically active INTRA, the nucleotide sequences encoding INTRA or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding INTRA. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding INTRA. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding INTRA and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) Results Probl. Cell Differ. 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding INTRA and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding INTRA. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. (See, e.g., Sambrook, supra; Ausubel, supra; Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509; Bitter, G.A. et al. (1987) Methods Enzymol. 153:516-544; Scorer, C.A. et al. (1994) Bio/Technology 12:181-184; Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945; Takamatsu, N. (1987) EMBO J. 6:307-311; Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105; The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill. New York NY, pp. 191-196; Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659; and Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.) Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. (See, e.g., Di Nicola, M. et al. (1998) Cancer Gen. Ther. 5(6):350-356; Yu, M. et al., (1993) Proc. Natl. Acad. Sci. USA 90(13):6340-6344; Buller, R.M. et al. (1985) Nature 317(6040):813-815; McGregor, D.P. et al. (1994) Mol. Immunol. 31(3):219-226; and Verma, I.M. and N. Somia (1997) Nature 389:239-242.) The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding INTRA. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding INTRA can be achieved using a multifunctional E. coli vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPORT1 plasmid (Life Technologies). Ligation of sequences encoding INTRA into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for in vitro transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of INTRA are needed, e.g. for the production of antibodies, vectors which direct high level expression of INTRA may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of INTRA. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH

promoters, may be used in the yeast Saccharomyces cerevisiae or Pichia pastoris. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, supra; Bitter, supra; and Scorer, supra.)

Plant systems may also be used for expression of INTRA. Transcription of sequences encoding INTRA may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, supra; Broglie, supra; and Winter, supra.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding INTRA may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses INTRA in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of INTRA in cell lines is preferred. For example, sequences encoding INTRA can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk*⁻ and *aprˉ* cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides neomycin and G-418; and *als* and *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), ß glucuronidase and its substrate ß-glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding INTRA is inserted within a marker gene sequence, transformed cells containing sequences encoding INTRA can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding INTRA under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding INTRA and that express INTRA may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of INTRA using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on INTRA is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St. Paul MN, Sect. IV; Coligan, J.E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and

Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ.)

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding INTRA include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding INTRA, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding INTRA may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode INTRA may be designed to contain signal sequences which direct secretion of INTRA through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" or "pro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38) are available from the American Type Culture Collection (ATCC, Manassas VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding INTRA may be ligated to a heterologous sequence resulting in translation of a fusion protein in any of the aforementioned host systems. For example, a chimeric INTRA protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of INTRA activity. Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available

affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the INTRA encoding sequence and the heterologous protein sequence, so that INTRA may be cleaved away from the heterologous moiety following purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, sup. a, ch. 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled INTRA may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract system (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, for example, ^{35}S-methionine.

INTRA of the present invention or fragments thereof may be used to screen for compounds that specifically bind to INTRA. At least one and up to a plurality of test compounds may be screened for specific binding to INTRA. Examples of test compounds include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

In one embodiment, the compound thus identified is closely related to the natural ligand of INTRA, e.g., a ligand or fragment thereof, a natural substrate, a structural or functional mimetic, or a natural binding partner. (See, Coligan, J.E. et al. (1991) Current Protocols in Immunology 1(2): Chapter 5.) Similarly, the compound can be closely related to the natural receptor to which INTRA binds, or to at least a fragment of the receptor, e.g., the ligand binding site. In either case, the compound can be rationally designed using known techniques. In one embodiment, screening for these compounds involves producing appropriate cells which express INTRA, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, Drosophila, or E. coli. Cells expressing INTRA or cell membrane fractions which contain INTRA are then contacted with a test compound and binding, stimulation, or inhibition of activity of either INTRA or the compound is analyzed.

An assay may simply test binding of a test compound to the polypeptide, wherein binding is detected by a fluorophore, radioisotope, enzyme conjugate, or other detectable label. For example, the assay may comprise the steps of combining at least one test compound with INTRA, either in

solution or affixed to a solid support, and detecting the binding of INTRA to the compound. Alternatively, the assay may detect or measure binding of a test compound in the presence of a labeled competitor. Additionally, the assay may be carried out using cell-free preparations, chemical libraries, or natural product mixtures, and the test compound(s) may be free in solution or affixed to a solid support.

INTRA of the present invention or fragments thereof may be used to screen for compounds that modulate the activity of INTRA. Such compounds may include agonists, antagonists, or partial or inverse agonists. In one embodiment, an assay is performed under conditions permissive for INTRA activity, wherein INTRA is combined with at least one test compound, and the activity of INTRA in the presence of a test compound is compared with the activity of INTRA in the absence of the test compound. A change in the activity of INTRA in the presence of the test compound is indicative of a compound that modulates the activity of INTRA. Alternatively, a test compound is combined with an in vitro or cell-free system comprising INTRA under conditions suitable for INTRA activity, and the assay is performed. In either of these assays, a test compound which modulates the activity of INTRA may do so indirectly and need not come in direct contact with the test compound. At least one and up to a plurality of test compounds may be screened.

In another embodiment, polynucleotides encoding INTRA or their mammalian homologs may be "knocked out" in an animal model system using homologous recombination in embryonic stem (ES) cells. Such techniques are well known in the art and are useful for the generation of animal models of human disease. (See, e.g., U.S. Patent No. 5,175,383 and U.S. Patent No. 5,767,337.) For example, mouse ES cells, such as the mouse 129/SvJ cell line, are derived from the early mouse embryo and grown in culture. The ES cells are transformed with a vector containing the gene of interest disrupted by a marker gene, e.g., the neomycin phosphotransferase gene (neo; Capecchi, M.R. (1989) Science 244:1288-1292). The vector integrates into the corresponding region of the host genome by homologous recombination. Alternatively, homologous recombination takes place using the Cre-loxP system to knockout a gene of interest in a tissue- or developmental stage-specific manner (Marth, J.D. (1996) Clin. Invest. 97:1999-2002; Wagner, K.U. et al. (1997) Nucleic Acids Res. 25:4323-4330). Transformed ES cells are identified and microinjected into mouse cell blastocysts such as those from the C57BL/6 mouse strain. The blastocysts are surgically transferred to pseudopregnant dams, and the resulting chimeric progeny are genotyped and bred to produce heterozygous or homozygous strains. Transgenic animals thus generated may be tested with potential therapeutic or toxic agents.

Polynucleotides encoding INTRA may also be manipulated in vitro in ES cells derived from human blastocysts. Human ES cells have the potential to differentiate into at least eight separate cell lineages including endoderm, mesoderm, and ectodermal cell types. These cell lineages differentiate

into, for example, neural cells, hematopoietic lineages, and cardiomyocytes (Thomson, J.A. et al. (1998) Science 282:1145-1147).

Polynucleotides encoding INTRA can also be used to create "knockin" humanized animals (pigs) or transgenic animals (mice or rats) to model human disease. With knockin technology, a region of a polynucleotide encoding INTRA is injected into animal ES cells, and the injected sequence integrates into the animal cell genome. Transformed cells are injected into blastulae, and the blastulae are implanted as described above. Transgenic progeny or inbred lines are studied and treated with potential pharmaceutical agents to obtain information on treatment of a human disease. Alternatively, a mammal inbred to overexpress INTRA, e.g., by secreting INTRA in its milk, may also serve as a convenient source of that protein (Janne, J. et al. (1998) Biotechnol. Annu. Rev. 4:55-74).

THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of INTRA and intracellular signaling molecules. In addition, the expression of INTRA is closely associated with cancers of the hematopoetic/immune, nervous, gastrointestinal, and reproductive, systems therefore, INTRA appears to play a role in cell proliferative, autoimmune/inflammatory, neurological, gastrointestinal, reproductive, and developmental disorders. In the treatment of disorders associated with increased INTRA expression or activity, it is desirable to decrease the expression or activity of INTRA. In the treatment of disorders associated with decreased INTRA expression or activity, it is desirable to increase the expression or activity of INTRA.

Therefore, in one embodiment, INTRA or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of INTRA. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, hematopoietic cancer including lymphoma, leukemia, and myeloma; and other cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, adenoma, carcinoma and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an autoimmune/inflammatory disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's

disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; and a gastrointestinal disorder such as dysphagia, peptic esophagitis, esophageal spasm, esophageal stricture, esophageal carcinoma, dyspepsia, indigestion, gastritis, gastric carcinoma, anorexia, nausea, emesis, gastroparesis, antral or pyloric edema, abdominal angina, pyrosis, gastroenteritis, intestinal obstruction, infections of the intestinal tract, peptic ulcer, cholelithiasis, cholecystitis, cholestasis, pancreatitis, pancreatic carcinoma, biliary tract disease, hepatitis, hyperbilirubinemia, cirrhosis, passive congestion of the liver, hepatoma, infectious colitis, ulcerative colitis, ulcerative proctitis, Crohn's disease, Whipple's disease, Mallory-Weiss syndrome, colonic carcinoma, colonic obstruction, irritable bowel syndrome, short bowel syndrome, diarrhea, constipation, gastrointestinal hemorrhage, acquired immunodeficiency syndrome (AIDS) enteropathy, jaundice, hepatic encephalopathy, hepatorenal syndrome, hepatic steatosis, hemochromatosis, Wilson's disease, alpha$_1$-antitrypsin deficiency, Reye's syndrome, primary sclerosing cholangitis, liver infarction, portal vein obstruction and thrombosis, centrilobular necrosis, peliosis hepatis, hepatic vein thrombosis, veno-occlusive disease, preeclampsia, eclampsia, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, and a hepatic tumor including a nodular hyperplasia,.a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system

disorders, dermatomyositis and polymyositis, inherited, metabolic, endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic disorders, akathesia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, and Tourette's disorder; and a gastrointestinal disorder such as esophagitis, esophageal carcinoma, gastritis, gastric carcinoma, inflammatory bowel disease, cholecystitis, infections of the intestinal tract, pancreatitis, pancreatic carcinoma, cirrhosis, hepatitis, hepatoma, colitis, colonic carcinoma, and Crohn's disease.

In another embodiment, a vector capable of expressing INTRA or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of INTRA including, but not limited to, those described above.

In a further embodiment, a pharmaceutical composition comprising a substantially purified INTRA in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of INTRA including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of INTRA may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of INTRA including, but not limited to, those listed above.

In a further embodiment, an antagonist of INTRA may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of INTRA. Examples of such disorders include, but are not limited to, those cell proliferative, autoimmune/inflammatory, neurological, gastrointestinal, reproductive, and developmental disorders described above. In one aspect, an antibody which specifically binds INTRA may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express INTRA.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding INTRA may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of INTRA including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of INTRA may be produced using methods which are generally known in the art. In particular, purified INTRA may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind INTRA. Antibodies to INTRA may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are generally preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with INTRA or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to INTRA have an amino acid sequence consisting of at least about 5 amino acids, and generally will consist of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein. Short stretches of INTRA amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to INTRA may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. USA 80:2026-2030; and Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. USA 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce INTRA-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton, D.R. (1991) Proc. Natl. Acad. Sci. USA 88:10134-10137.)

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. USA 86:3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for INTRA may also be generated. For example, such fragments include, but are not limited to, $F(ab')_2$ fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the F(ab')2 fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between INTRA and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering INTRA epitopes is generally used, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for INTRA. Affinity is expressed as an association constant, K_a, which is defined as the molar concentration of INTRA-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K_a determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple INTRA epitopes, represents the average affinity, or avidity, of the antibodies for INTRA. The K_a determined for a preparation of monoclonal antibodies, which are monospecific for a particular INTRA epitope, represents a true measure of affinity. High-affinity antibody preparations with K_a ranging from about 10^9 to 10^{12} L/mole are preferred for use in immunoassays in which the INTRA-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K_a ranging from about 10^6 to 10^7 L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of INTRA, preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington DC; Liddell, J.E. and A. Cryer (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml,

preferably 5-10 mg specific antibody/ml, is generally employed in procedures requiring precipitation of INTRA-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al., supra.)

In another embodiment of the invention, the polynucleotides encoding INTRA, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, modifications of gene expression can be achieved by designing complementary sequences or antisense molecules (DNA, RNA, PNA, or modified oligonucleotides) to the coding or regulatory regions of the gene encoding INTRA. Such technology is well known in the art, and antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding INTRA. (See, e.g., Agrawal, S., ed. (1996) Antisense Therapeutics, Humana Press Inc., Totawa NJ.)

In therapeutic use, any gene delivery system suitable for introduction of the antisense sequences into appropriate target cells can be used. Antisense sequences can be delivered intracellularly in the form of an expression plasmid which, upon transcription, produces a sequence complementary to at least a portion of the cellular sequence encoding the target protein. (See, e.g., Slater, J.E. et al. (1998) J. Allergy Clin. Immunol. 102(3):469-475; and Scanlon, K.J. et al. (1995) 9(13):1288-1296.) Antisense sequences can also be introduced intracellularly through the use of viral vectors, such as retrovirus and adeno-associated virus vectors. (See, e.g., Miller, A.D. (1990) Blood 76:271; Ausubel, supra; Uckert, W. and W. Walther (1994) Pharmacol. Ther. 63(3):323-347.) Other gene delivery mechanisms include liposome-derived systems, artificial viral envelopes, and other systems known in the art. (See, e.g., Rossi, J.J. (1995) Br. Med. Bull. 51(1):217-225; Boado, R.J. et al. (1998) J. Pharm. Sci. 87(11):1308-1315; and Morris, M.C. et al. (1997) Nucleic Acids Res. 25(14):2730-2736.)

In another embodiment of the invention, polynucleotides encoding INTRA may be used for somatic or germline gene therapy. Gene therapy may be performed to (i) correct a genetic deficiency (e.g., in the cases of severe combined immunodeficiency (SCID)-X1 disease characterized by X-linked inheritance (Cavazzana-Calvo, M. et al. (2000) Science 288:669-672), severe combined immunodeficiency syndrome associated with an inherited adenosine deaminase (ADA) deficiency (Blaese, R.M. et al. (1995) Science 270:475-480; Bordignon, C. et al. (1995) Science 270:470-475), cystic fibrosis (Zabner, J. et al. (1993) Cell 75:207-216; Crystal, R.G. et al. (1995) Hum. Gene Therapy 6:643-666; Crystal, R.G. et al. (1995) Hum. Gene Therapy 6:667-703), thalassamias, familial hypercholesterolemia, and hemophilia resulting from Factor VIII or Factor IX deficiencies (Crystal, R.G. (1995) Science 270:404-410; Verma, I.M. and Somia, N. (1997) Nature 389:239-242)), (ii) express a conditionally lethal gene product (e.g., in the case of cancers which result from unregulated

cell proliferation), or (iii) express a protein which affords protection against intracellular parasites (e.g., against human retroviruses, such as human immunodeficiency virus (HIV) (Baltimore, D. (1988) Nature 335:395-396; Poeschla, E. et al. (1996) Proc. Natl. Acad. Sci. USA. 93:11395-11399), hepatitis B or C virus (HBV, HCV); fungal parasites, such as Candida albicans and Paracoccidioides brasiliensis; and protozoan parasites such as Plasmodium falciparum and Trypanosoma cruzi). In the case where a genetic deficiency in INTRA expression or regulation causes disease, the expression of INTRA from an appropriate population of transduced cells may alleviate the clinical manifestations caused by the genetic deficiency.

In a further embodiment of the invention, diseases or disorders caused by deficiencies in INTRA are treated by constructing mammalian expression vectors encoding INTRA and introducing these vectors by mechanical means into INTRA-deficient cells. Mechanical transfer technologies for use with cells in vivo or ex vitro include (i) direct DNA microinjection into individual cells, (ii) ballistic gold particle delivery, (iii) liposome-mediated transfection, (iv) receptor-mediated gene transfer, and (v) the use of DNA transposons (Morgan, R.A. and W.F. Anderson (1993) Annu. Rev. Biochem. 62:191-217; Ivics, Z. (1997) Cell 91:501-510; Boulay, J-L. and H. Récipon (1998) Curr. Opin. Biotechnol. 9:445-450).

Expression vectors that may be effective for the expression of INTRA include, but are not limited to, the PCDNA 3.1, EPITAG, PRCCMV2, PREP, PVAX vectors (Invitrogen, Carlsbad CA), PCMV-SCRIPT, PCMV-TAG, PEGSH/PERV (Stratagene, La Jolla CA), and PTET-OFF, PTET-ON, PTRE2, PTRE2-LUC, PTK-HYG (Clontech, Palo Alto CA). INTRA may be expressed using (i) a constitutively active promoter, (e.g., from cytomegalovirus (CMV), Rous sarcoma virus (RSV). SV40 virus, thymidine kinase (TK), or β-actin genes), (ii) an inducible promoter (e.g., the tetracycline-regulated promoter (Gossen, M. and H. Bujard (1992) Proc. Natl. Acad. Sci. U.S.A. 89:5547-5551; Gossen, M. et al. (1995) Science 268:1766-1769; Rossi, F.M.V. and H.M. Blau (1998) Curr. Opin. Biotechnol. 9:451-456), commercially available in the T-REX plasmid (Invitrogen)); the ecdysone-inducible promoter (available in the plasmids PVGRXR and PIND; Invitrogen); the FK506/rapamycin inducible promoter; or the RU486/mifepristone inducible promoter (Rossi, F.M.V. and H.M. Blau, supra)), or (iii) a tissue-specific promoter or the native promoter of the endogenous gene encoding INTRA from a normal individual.

Commercially available liposome transformation kits (e.g., the PERFECT LIPID TRANSFECTION KIT, available from Invitrogen) allow one with ordinary skill in the art to deliver polynucleotides to target cells in culture and require minimal effort to optimize experimental parameters. In the alternative, transformation is performed using the calcium phosphate method (Graham, F.L. and A.J. Eb (1973) Virology 52:456-467), or by electroporation (Neumann, E. et al.

(1982) EMBO J. 1:841-845). The introduction of DNA to primary cells requires modification of these standardized mammalian transfection protocols.

In another embodiment of the invention, diseases or disorders caused by genetic defects with respect to INTRA expression are treated by constructing a retrovirus vector consisting of (i) the polynucleotide encoding INTRA under the control of an independent promoter or the retrovirus long terminal repeat (LTR) promoter, (ii) appropriate RNA packaging signals, and (iii) a Rev-responsive element (RRE) along with additional retrovirus *cis*-acting RNA sequences and coding sequences required for efficient vector propagation. Retrovirus vectors (e.g., PFB and PFBNEO) are commercially available (Stratagene) and are based on published data (Riviere, I. et al. (1995) Proc. Natl. Acad. Sci. U.S.A. 92:6733-6737), incorporated by reference herein. The vector is propagated in an appropriate vector producing cell line (VPCL) that expresses an envelope gene with a tropism for receptors on the target cells or a promiscuous envelope protein such as VSVg (Armentano, D. et al. (1987) J. Virol. 61:1647-1650; Bender, M.A. et al. (1987) J. Virol. 61:1639-1646; Adam, M.A. and A.D. Miller (1988) J. Virol. 62:3802-3806; Dull, T. et al. (1998) J. Virol. 72:8463-8471; Zufferey, R. et al. (1998) J. Virol. 72:9873-9880). U.S. Patent Number 5,910,434 to Rigg ("Method for obtaining retrovirus packaging cell lines producing high transducing efficiency retroviral supernatant") discloses a method for obtaining retrovirus packaging cell lines and is hereby incorporated by reference. Propagation of retrovirus vectors, transduction of a population of cells (e.g., CD4+ T-cells), and the return of transduced cells to a patient are procedures well known to persons skilled in the art of gene therapy and have been well documented (Ranga, U. et al. (1997) J. Virol. 71:7020-7029; Bauer, G. et al. (1997) Blood 89:2259-2267; Bonyhadi, M.L. (1997) J. Virol. 71:4707-4716; Ranga, U. et al. (1998) Proc. Natl. Acad. Sci. U.S.A. 95:1201-1206; Su, L. (1997) Blood 89:2283-2290).

In the alternative, an adenovirus-based gene therapy delivery system is used to deliver polynucleotides encoding INTRA to cells which have one or more genetic abnormalities with respect to the expression of INTRA. The construction and packaging of adenovirus-based vectors are well known to those with ordinary skill in the art. Replication defective adenovirus vectors have proven to be versatile for importing genes encoding immunoregulatory proteins into intact islets in the pancreas (Csete, M.E. et al. (1995) Transplantation 27:263-268). Potentially useful adenoviral vectors are described in U.S. Patent Number 5,707,618 to Armentano ("Adenovirus vectors for gene therapy"), hereby incorporated by reference. For adenoviral vectors, see also Antinozzi, P.A. et al. (1999) Annu. Rev. Nutr. 19:511-544; and Verma, I.M. and N. Somia (1997) Nature 18:389:239-242, both incorporated by reference herein.

In another alternative, a herpes-based, gene therapy delivery system is used to deliver polynucleotides encoding INTRA to target cells which have one or more genetic abnormalities with

respect to the expression of INTRA. The use of herpes simplex virus (HSV)-based vectors may be especially valuable for introducing INTRA to cells of the central nervous system, for which HSV has a tropism. The construction and packaging of herpes-based vectors are well known to those with ordinary skill in the art. A replication-competent herpes simplex virus (HSV) type 1-based vector has been used to deliver a reporter gene to the eyes of primates (Liu, X. et al. (1999) Exp. Eye Res.169:385-395). The construction of a HSV-1 virus vector has also been disclosed in detail in U.S. Patent Number 5,804,413 to DeLuca ("Herpes simplex virus strains for gene transfer"), which is hereby incorporated by reference. U.S. Patent Number 5,804,413 teaches the use of recombinant HSV d92 which consists of a genome containing at least one exogenous gene to be transferred to a cell under the control of the appropriate promoter for purposes including human gene therapy. Also taught by this patent are the construction and use of recombinant HSV strains deleted for ICP4, ICP27 and ICP22. For HSV vectors, see also Goins, W.F. et al. (1999) J. Virol. 73:519-532 and Xu, H. et al. (1994) Dev. Biol. 163:152-161, hereby incorporated by reference. The manipulation of cloned herpesvirus sequences, the generation of recombinant virus following the transfection of multiple plasmids containing different segments of the large herpesvirus genomes, the growth and propagation of herpesvirus, and the infection of cells with herpesvirus are techniques well known to those of ordinary skill in the art.

In another alternative, an alphavirus (positive, single-stranded RNA virus) vector is used to deliver polynucleotides encoding INTRA to target cells. The biology of the prototypic alphavirus, Semliki Forest Virus (SFV), has been studied extensively and gene transfer vectors have been based on the SFV genome (Garoff, H. and K.-J. Li (1998) Curr. Opin. Biotech. 9:464-469). During alphavirus RNA replication, a subgenomic RNA is generated that normally encodes the viral capsid proteins. This subgenomic RNA replicates to higher levels than the full-length genomic RNA, resulting in the overproduction of capsid proteins relative to the viral proteins with enzymatic activity (e.g., protease and polymerase). Similarly, inserting the coding sequence for INTRA into the alphavirus genome in place of the capsid-coding region results in the production of a large number of INTRA-coding RNAs and the synthesis of high levels of INTRA in vector transduced cells. While alphavirus infection is typically associated with cell lysis within a few days, the ability to establish a persistent infection in hamster normal kidney cells (BHK-21) with a variant of Sindbis virus (SIN) indicates that the lytic replication of alphaviruses can be altered to suit the needs of the gene therapy application (Dryga, S.A. et al. (1997) Virology 228:74-83). The wide host range of alphaviruses will allow the introduction of INTRA into a variety of cell types. The specific transduction of a subset of cells in a population may require the sorting of cells prior to transduction. The methods of manipulating infectious cDNA clones of alphaviruses, performing alphavirus cDNA and RNA

transfections, and performing alphavirus infections, are well known to those with ordinary skill in the art.

Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, may also be employed to inhibit gene expression. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding INTRA.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding INTRA. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs

and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

An additional embodiment of the invention encompasses a method for screening for a compound which is effective in altering expression of a polynucleotide encoding INTRA. Compounds which may be effective in altering expression of a specific polynucleotide may include, but are not limited to, oligonucleotides, antisense oligonucleotides, triple helix-forming oligonucleotides, transcription factors and other polypeptide transcriptional regulators, and non-macromolecular chemical entities which are capable of interacting with specific polynucleotide sequences. Effective compounds may alter polynucleotide expression by acting as either inhibitors or promoters of polynucleotide expression. Thus, in the treatment of disorders associated with increased INTRA expression or activity, a compound which specifically inhibits expression of the polynucleotide encoding INTRA may be therapeutically useful, and in the treament of disorders associated with decreased INTRA expression or activity, a compound which specifically promotes expression of the polynucleotide encoding INTRA may be therapeutically useful.

At least one, and up to a plurality, of test compounds may be screened for effectiveness in altering expression of a specific polynucleotide. A test compound may be obtained by any method commonly known in the art, including chemical modification of a compound known to be effective in altering polynucleotide expression; selection from an existing, commercially-available or proprietary library of naturally-occurring or non-natural chemical compounds; rational design of a compound based on chemical and/or structural properties of the target polynucleotide; and selection from a library of chemical compounds created combinatorially or randomly. A sample comprising a polynucleotide encoding INTRA is exposed to at least one test compound thus obtained. The sample may comprise, for example, an intact or permeabilized cell, or an in vitro cell-free or reconstituted biochemical system. Alterations in the expression of a polynucleotide encoding INTRA are assayed by any method commonly known in the art. Typically, the expression of a specific nucleotide is detected by hybridization with a probe having a nucleotide sequence complementary to the sequence of the polynucleotide encoding INTRA. The amount of hybridization may be quantified, thus forming the basis for a comparison of the expression of the polynucleotide both with and without exposure to one or more test compounds. Detection of a change in the expression of a polynucleotide exposed to a test compound indicates that the test compound is effective in altering the expression of the polynucleotide. A screen for a compound effective in altering expression of a specific polynucleotide can be carried out, for example, using a Schizosaccharomyces pombe gene expression system (Atkins, D. et al. (1999) U.S. Patent No. 5,932,435; Arndt, G.M. et al. (2000) Nucleic Acids

Res. 28:E15) or a human cell line such as HeLa cell (Clarke. M.L. et al. (2000) Biochem. Biophys. Res. Commun. 268:8-13). A particular embodiment of the present invention involves screening a combinatorial library of oligonucleotides (such as deoxyribonucleotides, ribonucleotides, peptide nucleic acids, and modified oligonucleotides) for antisense activity against a specific polynucleotide sequence (Bruice, T.W. et al. (1997) U.S. Patent No. 5,686,242; Bruice, T.W. et al. (2000) U.S. Patent No. 6,022,691).

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nat. Biotechnol. 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as humans, dogs, cats, cows, horses, rabbits, and monkeys.

An additional embodiment of the invention relates to the administration of a pharmaceutical composition which generally comprises an active ingredient formulated with a pharmaceutically acceptable excipient. Excipients may include, for example, sugars, starches, celluloses, gums, and proteins. Various formulations are commonly known and are thoroughly discussed in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA). Such pharmaceutical compositions may consist of INTRA, antibodies to INTRA, and mimetics, agonists, antagonists, or inhibitors of INTRA.

The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, pulmonary, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

Pharmaceutical compositions for pulmonary administration may be prepared in liquid or dry powder form. These compositions are generally aerosolized immediately prior to inhalation by the patient. In the case of small molecules (e.g. traditional low molecular weight organic drugs), aerosol delivery of fast-acting formulations is well-known in the art. In the case of macromolecules (e.g. larger peptides and proteins), recent developments in the field of pulmonary delivery via the alveolar region of the lung have enabled the practical delivery of drugs such as insulin to blood circulation (see, e.g., Patton. J.S. et al., U.S. Patent No. 5,997,848). Pulmonary delivery has the advantage of administration without needle injection, and obviates the need for potentially toxic penetration enhancers.

Pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

Specialized forms of pharmaceutical compositions may be prepared for direct intracellular delivery of macromolecules comprising INTRA or fragments thereof. For example, liposome preparations containing a cell-impermeable macromolecule may promote cell fusion and intracellular delivery of the macromolecule. Alternatively, INTRA or a fragment thereof may be joined to a short cationic N-terminal portion from the HIV Tat-1 protein. Fusion proteins thus generated have been found to transduce into the cells of all tissues, including the brain, in a mouse model system (Schwarze, S.R. et al. (1999) Science 285:1569-1572).

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models such as mice, rats, rabbits, dogs, monkeys, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example INTRA or fragments thereof, antibodies of INTRA, and agonists, antagonists or inhibitors of INTRA, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED_{50} (the dose therapeutically effective in 50% of the population) or LD_{50} (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the LD_{50}/ED_{50} ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from about 0.1 μg to 100.000 μg, up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

DIAGNOSTICS

In another embodiment, antibodies which specifically bind INTRA may be used for the diagnosis of disorders characterized by expression of INTRA, or in assays to monitor patients being treated with INTRA or agonists, antagonists, or inhibitors of INTRA. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for INTRA include methods which utilize the antibody and a label to detect INTRA in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring INTRA, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of INTRA expression. Normal or standard values for INTRA expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, for example, human subjects, with antibody to INTRA under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of INTRA expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding INTRA may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantify gene expression in biopsied tissues in which expression of INTRA may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of INTRA, and to monitor regulation of INTRA levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding INTRA or closely related molecules may be used to identify nucleic acid sequences which encode INTRA. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification will determine whether the

probe identifies only naturally occurring sequences encoding INTRA, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and may have at least 50% sequence identity to any of the INTRA encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:53-104 or from genomic sequences including promoters, enhancers, and introns of the INTRA gene.

Means for producing specific hybridization probes for DNAs encoding INTRA include the cloning of polynucleotide sequences encoding INTRA or INTRA derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as ^{32}P or ^{35}S, or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding INTRA may be used for the diagnosis of disorders associated with expression of INTRA. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, hematopoietic cancer including lymphoma, leukemia, and myeloma; and other cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, adenoma, carcinoma and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus ; an autoimmune/inflammatory disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal

circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma ; and a gastrointestinal disorder such as dysphagia, peptic esophagitis, esophageal spasm, esophageal stricture, esophageal carcinoma, dyspepsia, indigestion, gastritis, gastric carcinoma, anorexia, nausea, emesis, gastroparesis, antral or pyloric edema, abdominal angina, pyrosis, gastroenteritis, intestinal obstruction, infections of the intestinal tract, peptic ulcer, cholelithiasis, cholecystitis, cholestasis, pancreatitis, pancreatic carcinoma, biliary tract disease, hepatitis, hyperbilirubinemia, cirrhosis, passive congestion of the liver, hepatoma, infectious colitis, ulcerative colitis, ulcerative proctitis, Crohn's disease, Whipple's disease, Mallory-Weiss syndrome, colonic carcinoma, colonic obstruction, irritable bowel syndrome, short bowel syndrome, diarrhea, constipation, gastrointestinal hemorrhage, acquired immunodeficiency syndrome (AIDS) enteropathy, jaundice, hepatic encephalopathy, hepatorenal syndrome, hepatic steatosis, hemochromatosis, Wilson's disease, alpha$_1$-antitrypsin deficiency, Reye's syndrome, primary sclerosing cholangitis, liver infarction, portal vein obstruction and thrombosis, centrilobular necrosis, peliosis hepatis, hepatic vein thrombosis, veno-occlusive disease, preeclampsia, eclampsia, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, and a hepatic tumor including a nodular hyperplasia,.a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system disorders, dermatomyositis and polymyositis, inherited, metabolic, endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic disorders, akathesia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, and Tourette's disorder; and a gastrointestinal disorder such as esophagitis, esophageal carcinoma, gastritis, gastric carcinoma, inflammatory bowel disease, cholecystitis, infections of the intestinal tract, pancreatitis, pancreatic carcinoma, cirrhosis, hepatitis, hepatoma, colitis, colonic carcinoma, and Crohn's disease. The polynucleotide sequences encoding INTRA may be used in Southern or northern analysis, dot blot, or other membrane-based

technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered INTRA expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding INTRA may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding INTRA may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantified and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding INTRA in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of INTRA, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding INTRA, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding INTRA may involve the use of PCR. These oligomers may be chemically synthesized, generated

enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding INTRA, or a fragment of a polynucleotide complementary to the polynucleotide encoding INTRA, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or quantification of closely related DNA or RNA sequences.

In a particular aspect, oligonucleotide primers derived from the polynucleotide sequences encoding INTRA may be used to detect single nucleotide polymorphisms (SNPs). SNPs are substitutions, insertions and deletions that are a frequent cause of inherited or acquired genetic disease in humans. Methods of SNP detection include, but are not limited to, single-stranded conformation polymorphism (SSCP) and fluorescent SSCP (fSSCP) methods. In SSCP, oligonucleotide primers derived from the polynucleotide sequences encoding INTRA are used to amplify DNA using the polymerase chain reaction (PCR). The DNA may be derived, for example, from diseased or normal tissue, biopsy samples, bodily fluids, and the like. SNPs in the DNA cause differences in the secondary and tertiary structures of PCR products in single-stranded form, and these differences are detectable using gel electrophoresis in non-denaturing gels. In fSCCP, the oligonucleotide primers are fluorescently labeled, which allows detection of the amplimers in high-throughput equipment such as DNA sequencing machines. Additionally, sequence database analysis methods, termed in silico SNP (isSNP), are capable of identifying polymorphisms by comparing the sequence of individual overlapping DNA fragments which assemble into a common consensus sequence. These computer-based methods filter out sequence variations due to laboratory preparation of DNA and sequencing errors using statistical models and automated analyses of DNA sequence chromatograms. In the alternative, SNPs may be detected and characterized by mass spectrometry using, for example, the high throughput MASSARRAY system (Sequenom, Inc., San Diego CA).

Methods which may also be used to quantify the expression of INTRA include radiolabeling or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in a high-throughput format where the oligomer or polynucleotide of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as elements on a microarray. The microarray can be used in transcript imaging techniques which monitor the relative expression levels of large numbers of genes simultaneously as described in Seilhamer, J.J. et al., "Comparative Gene Transcript Analysis," U.S. Patent No. 5,840,484, incorporated herein by reference. The microarray may also be

used to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, to monitor progression/regression of disease as a function of gene expression, and to develop and monitor the activities of therapeutic agents in the treatment of disease. In particular, this information may be used to develop a pharmacogenomic profile of a patient in order to select the most appropriate and effective treatment regimen for that patient. For example, therapeutic agents which are highly effective and display the fewest side effects may be selected for a patient based on his/her pharmacogenomic profile.

In another embodiment, antibodies specific for INTRA, or INTRA or fragments thereof may be used as elements on a microarray. The microarray may be used to monitor or measure protein-protein interactions, drug-target interactions, and gene expression profiles, as described above.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. USA 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. USA 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.) Various types of microarrays are well known and thoroughly described in DNA Microarrays: A Practical Approach, M. Schena, ed. (1999) Oxford University Press, London, hereby expressly incorporated by reference.

In another embodiment of the invention, nucleic acid sequences encoding INTRA may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. Either coding or noncoding sequences may be used, and in some instances, noncoding sequences may be preferable over coding sequences. For example, conservation of a coding sequence among members of a multi-gene family may potentially cause undesired cross hybridization during chromosomal mapping. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.) Once mapped, the nucleic acid sequences of the invention may be used to develop genetic linkage maps, for example, which correlate the inheritance of a disease state with the inheritance of a particular chromosome region or restriction fragment length polymorphism (RFLP). (See, e.g., Lander, E.S. and D. Botstein (1986) Proc. Natl. Acad. Sci. USA 83:7353-7357.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man

(OMIM) World Wide Web site. Correlation between the location of the gene encoding INTRA on a physical map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder and thus may further positional cloning efforts.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the exact chromosomal locus is not known. This information is valuable to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the gene or genes responsible for a disease or syndrome have been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the instant invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, INTRA, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between INTRA and the agent being tested may be measured.

Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with INTRA, or fragments thereof, and washed. Bound INTRA is then detected by methods well known in the art. Purified INTRA can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding INTRA specifically compete with a test compound for binding INTRA. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with INTRA.

In additional embodiments, the nucleotide sequences which encode INTRA may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The disclosures of all patents, applications, and publications mentioned above and below, in particular U.S. Ser. No. 60/139,566 (filing date 16 June 1999), U.S. Ser. No. 60/149,640 (filing date 17 August 1999), and U.S. Ser. No. 60/164,417 (filing date 9 November 1999), are hereby expressly incorporated by reference.

EXAMPLES

I. Construction of cDNA Libraries

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In some cases, RNA was treated with DNase. For most libraries, poly(A+) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERSCRIPT plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units 5.1-6.6.) Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), PSPORT1 plasmid (Life Technologies), pcDNA2.1 plasmid (Invitrogen, Carlsbad CA), or pINCY plasmid (Incyte Genomics, Palo Alto CA). Recombinant

plasmids were transformed into competent E. coli cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5α, DH10B, or ElectroMAX DH10B from Life Technologies.

II. Isolation of cDNA Clones

Plasmids obtained as described in Example I were recovered from host cells by in vivo excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a FLUOROSKAN II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

III. Sequencing and Analysis

Incyte cDNA recovered in plasmids as described in Example II were sequenced as follows. Sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (PE Biosystems) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (PE Biosystems). Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 or 377 sequencing system (PE Biosystems) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example VI.

The polynucleotide sequences derived from cDNA sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those skilled in the art. Table 5 summarizes the tools, programs, and algorithms used and provides applicable descriptions, references, and threshold parameters. The first column of Table 5 shows the tools,

programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the score, the greater the homology between two sequences). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR). Polynucleotide and polypeptide sequence alignments were generated using the default parameters specified by the clustal algorithm as incorporated into the MEGALIGN multisequence alignment program (DNASTAR), which also calculates the percent identity between aligned sequences.

The polynucleotide sequences were validated by removing vector, linker, and polyA sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programing, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS, PRINTS, DOMO, PRODOM, and PFAM to acquire annotation using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS, DOMO, PRODOM, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probabilistic approach which analyzes consensus primary structures of gene families. (See, e.g., Eddy, S.R. (1996) Curr. Opin. Struct. Biol. 6:361-365.)

The programs described above for the assembly and analysis of full length polynucleotide and amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:53-104. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

IV. Analysis of Polynucleotide Expression

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel, 1995, supra, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in cDNA databases such as GenBank or LIFESEQ (Incyte Genomics). This analysis is

much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\text{BLAST Score} \times \text{Percent Identity}}{5 \times \text{minimum}\{\text{length(Seq. 1)}, \text{length(Seq. 2)}\}}$$

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. The product score is a normalized value between 0 and 100, and is calculated as follows: the BLAST score is multiplied by the percent nucleotide identity and the product is divided by (5 times the length of the shorter of the two sequences). The BLAST score is calculated by assigning a score of +5 for every base that matches in a high-scoring segment pair (HSP), and -4 for every mismatch. Two sequences may share more than one HSP (separated by gaps). If there is more than one HSP, then the pair with the highest BLAST score is used to calculate the product score. The product score represents a balance between fractional overlap and quality in a BLAST alignment. For example, a product score of 100 is produced only for 100% identity over the entire length of the shorter of the two sequences being compared. A product score of 70 is produced either by 100% identity and 70% overlap at one end, or by 88% identity and 100% overlap at the other. A product score of 50 is produced either by 100% identity and 50% overlap at one end, or 79% identity and 100% overlap.

The results of northern analyses are reported as a percentage distribution of libraries in which the transcript encoding INTRA occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation, trauma, cell proliferation, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table 3.

V. Chromosomal Mapping of ABBR Encoding Polynucleotides

The cDNA sequences which were used to assemble SEQ ID NO:8-14 were compared with sequences from the Incyte LIFESEQ database and public domain databases using BLAST and other implementations of the Smith-Waterman algorithm. Sequences from these databases that matched SEQ ID NO:8-14 were assembled into clusters of contiguous and overlapping sequences using assembly algorithms such as Phrap (Table 5). Radiation hybrid and genetic mapping data available from public resources such as the Stanford Human Genome Center (SHGC), Whitehead Institute for

Genome Research (WIGR), and Généthon were used to determine if any of the clustered sequences had been previously mapped. Inclusion of a mapped sequence in a cluster resulted in the assignment of all sequences of that cluster, including its particular SEQ ID NO:, to that map location.

The genetic map locations of SEQ ID NO:8-14 [fill in the specific SEQ ID NOs if not all of the sequences have been mapped] are described in The Invention as ranges, or intervals, of human chromosomes. [Include the following sentence if any of your sequences have more than one map location.] More than one map location is reported for SEQ ID NO:8-14 [fill in specific SEQ ID NO:s], indicating that previously mapped sequences having similarity, but not complete identity, to SEQ ID NO:8-14 [fill in specific SEQ ID NO:s] were assembled into their respective clusters. The map position of an interval, in centiMorgans, is measured relative to the terminus of the chromosome's p-arm. (The centiMorgan (cM) is a unit of measurement based on recombination frequencies between chromosomal markers. On average, 1 cM is roughly equivalent to 1 megabase (Mb) of DNA in humans, although this can vary widely due to hot and cold spots of recombination.) The cM distances are based on genetic markers mapped by Généthon which provide boundaries for radiation hybrid markers whose sequences were included in each of the clusters. Human genome maps and other resources available to the public, such as the NCBI "GeneMap'99" World Wide Web site (http://www.ncbi.nlm.nih.gov/genemap/), can be employed to determine if previously identified disease genes map within or in proximity to the intervals indicated above.

VI. Extension of INTRA Encoding Polynucleotides

The full length nucleic acid sequences of SEQ ID NO:53-104 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg^{2+}, $(NH_4)_2SO_4$, and β-mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C,

2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100 μl PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5 μl of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5 μl to 10 μl aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent E. coli cells. Transformed cells were selected on antibiotic-containing media, and individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethysulfoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (PE Biosystems).

In like manner, the polynucleotide sequences of SEQ ID NO:53-104 are used to obtain 5' regulatory sequences using the procedure above, along with oligonucleotides designed for such extension, and an appropriate genomic library.

VII. Labeling and Use of Individual Hybridization Probes

Hybridization probes derived from SEQ ID NO:53-104 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250 μCi of [γ-^{32}P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10^7 counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under conditions of up to, for example, 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are visualized using autoradiography or an alternative imaging means and compared.

VIII. Microarrays

The linkage or synthesis of array elements upon a microarray can be achieved utilizing photolithography, piezoelectric printing (ink-jet printing, See, e.g., Baldeschweiler, supra), mechanical microspotting technologies, and derivatives thereof. The substrate in each of the aforementioned technologies should be uniform and solid with a non-porous surface (Schena (1999), supra). Suggested substrates include silicon, silica, glass slides, glass chips, and silicon wafers. Alternatively, a procedure analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced using available methods and machines well known to those of ordinary skill in the art and may contain any appropriate number of elements. (See, e.g., Schena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645; Marshall, A. and J. Hodgson (1998) Nat. Biotechnol. 16:27-31.)

Full length cDNAs, Expressed Sequence Tags (ESTs), or fragments or oligomers thereof may comprise the elements of the microarray. Fragments or oligomers suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). The array elements are hybridized with polynucleotides in a biological sample. The polynucleotides in the biological sample are conjugated to a fluorescent label or other molecular tag for ease of detection. After hybridization, nonhybridized nucleotides from the biological sample are removed, and a

fluorescence scanner is used to detect hybridization at each array element. Alternatively, laser desorbtion and mass spectrometry may be used for detection of hybridization. The degree of complementarity and the relative abundance of each polynucleotide which hybridizes to an element on the microarray may be assessed. In one embodiment, microarray preparation and usage is described in detail below.

Tissue or Cell Sample Preparation

Total RNA is isolated from tissue samples using the guanidinium thiocyanate method and poly(A)$^+$ RNA is purified using the oligo-(dT) cellulose method. Each poly(A)$^+$ RNA sample is reverse transcribed using MMLV reverse-transcriptase, 0.05 pg/μl oligo-(dT) primer (21mer), 1X first strand buffer, 0.03 units/μl RNase inhibitor, 500 μM dATP, 500 μM dGTP, 500 μM dTTP, 40 μM dCTP, 40 μM dCTP-Cy3 (BDS) or dCTP-Cy5 (Amersham Pharmacia Biotech). The reverse transcription reaction is performed in a 25 ml volume containing 200 ng poly(A)$^+$ RNA with GEMBRIGHT kits (Incyte). Specific control poly(A)$^+$ RNAs are synthesized by in vitro transcription from non-coding yeast genomic DNA. After incubation at 37 °C for 2 hr, each reaction sample (one with Cy3 and another with Cy5 labeling) is treated with 2.5 ml of 0.5M sodium hydroxide and incubated for 20 minutes at 85 °C to the stop the reaction and degrade the RNA. Samples are purified using two successive CHROMA SPIN 30 gel filtration spin columns (CLONTECH Laboratories, Inc. (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated using 1 ml of glycogen (1 mg/ml), 60 ml sodium acetate, and 300 ml of 100% ethanol. The sample is then dried to completion using a SpeedVAC (Savant Instruments Inc., Holbrook NY) and resuspended in 14 μl 5X SSC/0.2% SDS.

Microarray Preparation

Sequences of the present invention are used to generate array elements. Each array element is amplified from bacterial cells containing vectors with cloned cDNA inserts. PCR amplification uses primers complementary to the vector sequences flanking the cDNA insert. Array elements are amplified in thirty cycles of PCR from an initial quantity of 1-2 ng to a final quantity greater than 5 μg. Amplified array elements are then purified using SEPHACRYL-400 (Amersham Pharmacia Biotech).

Purified array elements are immobilized on polymer-coated glass slides. Glass microscope slides (Corning) are cleaned by ultrasound in 0.1% SDS and acetone, with extensive distilled water washes between and after treatments. Glass slides are etched in 4% hydrofluoric acid (VWR Scientific Products Corporation (VWR), West Chester PA), washed extensively in distilled water, and coated with 0.05% aminopropyl silane (Sigma) in 95% ethanol. Coated slides are cured in a 110°C oven.

Array elements are applied to the coated glass substrate using a procedure described in US Patent No. 5.807,522. incorporated herein by reference. 1 μl of the array element DNA, at an average concentration of 100 ng/μl, is loaded into the open capillary printing element by a high-speed robotic apparatus. The apparatus then deposits about 5 nl of array element sample per slide.

Microarrays are UV-crosslinked using a STRATALINKER UV-crosslinker (Stratagene). Microarrays are washed at room temperature once in 0.2% SDS and three times in distilled water. Non-specific binding sites are blocked by incubation of microarrays in 0.2% casein in phosphate buffered saline (PBS) (Tropix, Inc., Bedford MA) for 30 minutes at 60 °C followed by washes in 0.2% SDS and distilled water as before.

Hybridization

Hybridization reactions contain 9 μl of sample mixture consisting of 0.2 μg each of Cy3 and Cy5 labeled cDNA synthesis products in 5X SSC, 0.2% SDS hybridization buffer. The sample mixture is heated to 65 °C for 5 minutes and is aliquoted onto the microarray surface and covered with an 1.8 cm^3 coverslip. The arrays are transferred to a waterproof chamber having a cavity just slightly larger than a microscope slide. The chamber is kept at 100% humidity internally by the addition of 140 μl of 5X SSC in a corner of the chamber. The chamber containing the arrays is incubated for about 6.5 hours at 60 °C. The arrays are washed for 10 min at 45 °C in a first wash buffer (1X SSC, 0.1% SDS), three times for 10 minutes each at 45 °C in a second wash buffer (0.1X SSC), and dried.

Detection

Reporter-labeled hybridization complexes are detected with a microscope equipped with an Innova 70 mixed gas 10 W laser (Coherent, Inc., Santa Clara CA) capable of generating spectral lines at 488 nm for excitation of Cy3 and at 632 nm for excitation of Cy5. The excitation laser light is focused on the array using a 20X microscope objective (Nikon, Inc., Melville NY). The slide containing the array is placed on a computer-controlled X-Y stage on the microscope and raster-scanned past the objective. The 1.8 cm x 1.8 cm array used in the present example is scanned with a resolution of 20 micrometers.

In two separate scans, a mixed gas multiline laser excites the two fluorophores sequentially. Emitted light is split, based on wavelength, into two photomultiplier tube detectors (PMT R1477, Hamamatsu Photonics Systems, Bridgewater NJ) corresponding to the two fluorophores. Appropriate filters positioned between the array and the photomultiplier tubes are used to filter the signals. The emission maxima of the fluorophores used are 565 nm for Cy3 and 650 nm for Cy5. Each array is typically scanned twice, one scan per fluorophore using the appropriate filters at the laser source, although the apparatus is capable of recording the spectra from both fluorophores simultaneously.

The sensitivity of the scans is typically calibrated using the signal intensity generated by a cDNA control species added to the sample mixture at a known concentration. A specific location on the array contains a complementary DNA sequence, allowing the intensity of the signal at that location to be correlated with a weight ratio of hybridizing species of 1:100,000. When two samples from different sources (e.g., representing test and control cells), each labeled with a different fluorophore, are hybridized to a single array for the purpose of identifying genes that are differentially expressed, the calibration is done by labeling samples of the calibrating cDNA with the two fluorophores and adding identical amounts of each to the hybridization mixture.

The output of the photomultiplier tube is digitized using a 12-bit RTI-835H analog-to-digital (A/D) conversion board (Analog Devices, Inc., Norwood MA) installed in an IBM-compatible PC computer. The digitized data are displayed as an image where the signal intensity is mapped using a linear 20-color transformation to a pseudocolor scale ranging from blue (low signal) to red (high signal). The data is also analyzed quantitatively. Where two different fluorophores are excited and measured simultaneously, the data are first corrected for optical crosstalk (due to overlapping emission spectra) between the fluorophores using each fluorophore's emission spectrum.

A grid is superimposed over the fluorescence signal image such that the signal from each spot is centered in each element of the grid. The fluorescence signal within each element is then integrated to obtain a numerical value corresponding to the average intensity of the signal. The software used for signal analysis is the GEMTOOLS gene expression analysis program (Incyte).

IX. Complementary Polynucleotides

Sequences complementary to the INTRA-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring INTRA. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of INTRA. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the INTRA-encoding transcript.

X. Expression of INTRA

Expression and purification of INTRA is achieved using bacterial or virus-based expression systems. For expression of INTRA in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac* (*tac*) hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory

element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express INTRA upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of INTRA in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding INTRA by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, INTRA is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from INTRA at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch. 10 and 16). Purified INTRA obtained by these methods can be used directly in the assays shown in Examples XI, XII, and XV.

XI. Demonstration of INTRA Activity

INTRA activity is associated with its ability to form protein-protein complexes and is measured by its ability to regulate growth characteristics of NIH3T3 mouse fibroblast cells. A cDNA encoding INTRA is subcloned into an appropriate eukaryotic expression vector. This vector is transfected into NIH3T3 cells using methods known in the art. Transfected cells are compared with non-transfected cells for the following quantifiable properties: growth in culture to high density, reduced attachment of cells to the substrate, altered cell morphology, and ability to induce tumors when injected into immunodeficient mice. The activity of INTRA is proportional to the extent of increased growth or frequency of altered cell morphology in NIH3T3 cells transfected with INTRA.

Alternatively, INTRA activity is measured by binding of INTRA to radiolabeled formin polypeptides containing the proline-rich region that specifically binds to SH3 containing proteins

(Chan. D.C. et al. (1996) EMBO J. 15: 1045-54). Samples of INTRA are run on SDS-PAGE gels, and transferred onto nitrocellulose by electroblotting. The blots are blocked for 1 hr at room temperature in TBST (137 mM NaCl, 2.7 mM Kcl, 25 mM Tris (pH 8.0) and 0.1% Tween-20) containing non-fat dry milk. Blots are then incubated with TBST containing the radioactive formin polypeptide for 4 hrs to overnight. After washing the blots four times with TBST, the blots are exposed to autoradiographic film. Radioactivity is quantitated by cutting out the radioactive spots and counting them in a radioisotope counter. The amount of radioactivity recovered is proportional to the activity of INTRA in the assay.

Alternatively, INTRA activity is demonstrated by measuring the binding of INTRA to Ca^{2+} using a Ca^{2+} overlay system (Weis, K. et al. (1994) J. Biol. Chem. 269:19142-19150). Purified INTRA is transferred and immobilized onto a nitrocellulose membrane. The membrane is washed three times with buffer (60 mM KCl, 5 mM $MgCl_2$, 10 mM imidazole-HCl, pH 6.8) and incubated in this buffer for 10 minutes with 1 μCi [$^{45}Ca^{2+}$] (NEN-DuPont, Boston, MA). Unbound [$^{45}Ca^{2+}$] is removed from the membrane by washing with water, and the membrane is dried. Membrane-bound [$^{45}Ca^{2+}$] is detected by autoradiography and quantified using image analysis systems and software. INTRA activity is proportional to the amount of [$^{45}Ca^{2+}$] detected on the membrane.

Alternatively, INTRA activity is assayed by measuring the conversion of ^{3}H-cAMP to ^{3}H-adenosine in the presence of INTRA and 5' nucleotidase. INTRA is added to a solution containing 50 mM Tris-HCl pH 7.5, 10 mM $MgCl^2$, 0.1 unit 5'nucleotidase (from Crotalus atrox venom), and 0.0064-2.0 uM ^{3}H- cAMP and the reaction is incubated at 37°C for a time period that would yield less than 15% cAMP hydrolysis in order to avoid non-linearity associated with product inhibition. Soluble radioactivity associated with ^{3}H-adenosine is quantitated using a Beta scintillation counter. The amount of radioactivity recovered is proportional to the activity of INTRA in the reaction.

XII. Functional Assays

INTRA function is assessed by expressing the sequences encoding INTRA at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT plasmid (Life Technologies) and pCR3.1 plasmid (Invitrogen), both of which contain the cytomegalovirus promoter. 5-10 μg of recombinant vector are transiently transfected into a human cell line, for example, an endothelial or hematopoietic cell line, using either liposome formulations or electroporation. 1-2 μg of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP;

Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the apoptotic state of the cells and other cellular properties. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M.G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of INTRA on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding INTRA and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding INTRA and other genes of interest can be analyzed by northern analysis or microarray techniques.

XIII. Production of INTRA Specific Antibodies

INTRA substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) Methods Enzymol. 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the INTRA amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, supra, ch. 11.)

Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A peptide synthesizer (PE Biosystems) using FMOC chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, supra.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide and anti-INTRA activity by, for example, binding the peptide or INTRA to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

XIV. Purification of Naturally Occurring INTRA Using Specific Antibodies

Naturally occurring or recombinant INTRA is substantially purified by immunoaffinity chromatography using antibodies specific for INTRA. An immunoaffinity column is constructed by covalently coupling anti-INTRA antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing INTRA are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of INTRA (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/INTRA binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and INTRA is collected.

XV. Identification of Molecules Which Interact with INTRA

INTRA, or biologically active fragments thereof, are labeled with ^{125}I Bolton-Hunter reagent. (See, e.g., Bolton A.E. and W.M. Hunter (1973) Biochem. J. 133:529-539.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled INTRA, washed, and any wells with labeled INTRA complex are assayed. Data obtained using different concentrations of INTRA are used to calculate values for the number, affinity, and association of INTRA with the candidate molecules.

Alternatively, molecules interacting with INTRA are analyzed using the yeast two-hybrid system as described in Fields, S. and O. Song (1989, Nature 340:245-246), or using commercially available kits based on the two-hybrid system, such as the MATCHMAKER system (Clontech).

INTRA may also be used in the PATHCALLING process (CuraGen Corp., New Haven CT) which employs the yeast two-hybrid system in a high-throughput manner to determine all interactions between the proteins encoded by two large libraries of genes (Nandabalan, K. et al. (2000) U.S. Patent No. 6,057,101).

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with certain embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

Table 1

Polypeptide SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
1	53	129042	TESTNOT01	129042H1 (TESTNOT01), 129042T6 (TESTNOT01), 594163H1 (BRAVUNT02), 137635J6 (LUNGNOT10), 1968641R6 (BRSTNOT04), 4193335F6 (BRAPDIT01), 5636985H1 (UTRSTMR01)
2	54	778003	COLNNOT05	778003H1 (COLNNOT05), 778003X29 (COLNNOT05),
3	55	1418671	KIDNNOT09	793138X17 (PROSTUT03), 553356ZH1 (HEARFET05) 458013F1 (KERANOT01), 461367R6 (KERANOT01), 1418671H1 (KIDNNOT09), 1418671X301D1 (KIDNNOT09), 1452670F1 (PENITUT01), 1455886F1 (COLNFET02), 2921431H1 (SININOT04)
4	56	1456841	COLNFET02	2141806X3 (STOMNOT01), 1456841H1 (COLNFET02), 1517021F1 (PANCTUT01), 2280709F6 (COLSUCT01), SBFA01757F1, SBFA04860F1, SBFA03431F1
5	57	2020010	CONNNOT01	520251R1 (MMLR2DT01), 552501H1 (SCORNOT01), 1297508H1 (BRSTNOT07), 1417085H1 (BRAINOT12), 1455946F1 (COLNFET02), 1864670H1 (PROSNOT19), 1922941R6 (BRSTTUT01), 1922941T6 (BRSTTUT01), 1930785H1 (COLNTUT03), 2020010F6 (CONNNOT01), 2020010H1 (CONNNOT01), 2879789H1 (UTRSTUT05), 3324110H1 (PTHYNOT03), 3766286H1 (BRSTNOT24), 4305754H1 (TESTTUT03)
6	58	2149037	BRAINOT09	1382860F1 (BRAITUT08), 1709135F6 (PROSNOT16), 1735155R6 (PITUNOT03), 1861076F6 (PROSNOT19), 2149037H1 (BRAINOT09), 2149037X15F1 (BRAINOT09), 2280356H1 (PROSNON01), 2524642F6 (BRAITUT21), 2590271H1 (LUNGNOT22), 2970418H2 (HEAONOT02), 3084127H1 (BRALFET01), 4789892T6 (EPIBUNT01)
7	59	2162179	ENDCNOT02	2162179F6 (ENDCNOT02), 2162179H1 (ENDCNOT02), 3865236H1 (BRATTUT07)
8	60	2244706	HIPONON02	2244706H1 (HIPONON02), 3272168F6 (BRAINOT20), SBWA00950V1, SBWA03641V1, SBWA02322V1

Table 1 (cont.)

Polypeptide SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
9	61	2316805	OVARNOT02	363271R6 (PROSNOT01), 855363H1 (NGANNOT01), 1209030T1 (BRSTNOT02), 1265148R1 (SYNORAT05), 1294807F1 (PGANNOT03), 1351585F1 (LATRTUT02), 1852006F6 (LUNGFET03), 2316805H1 (OVARNOT02), 2320867H1 (OVARNOT02), 3563231F6 (SKINNOT05)
10	62	2320010	OVARNOT02	448783H1 (TLYMNOT02), 470134R1 (MMLR1DT01), 720124F1 (SYNOOAT01), 1873477F6 (LEUKNOT02), 2320010H1 (OVARNOT02), 3049510T6 (LUNGNOT25), 3087109F6 (HEAONOT03), 4144881H1 (SINITUT04), 5089346H1 (UTRSTMR01)
11	63	2564901	ADRETUT01	214410F1 (STOMNOT01), 927356R1 (BRAINOT04), 2564901H1 (ADRETUT01)
12	64	2615168	GBLANOT01	1445950F6 (PLACNOT02), 2615168H1 (GBLANOT01), 2746963F6 (LUNGTUT11), 2746963T6 (LUNGTUT11), 3250984H1 (SEMVNOT03), 3459378H1 (293TF1T01), 3831615H1 (PANCNOT17), 4334378H1 (KIDCTMT01), 4818908H1 (PROSTUT17)
13	65	2658329	LUNGTUT09	1210539H1 (BRSTNOT02), 1210539R6 (BRSTNOT02), 1985147R6.comp (LUNGAST01), 2311120R6 (NGANNOT01), 2658329H1 (LUNGTUT09), 2717243F6 (THYRNOT09), 2831384F7 (TLYMNOT03), 3846358H1 (DENDNOT01), 4898171H1 (OVARDIT01)
14	66	2708944	PONSAZT01	309840R6 (TMLR2DT01), 1241166R6 (LUNGNOT03), 1381850H1 (BRAITUT08), 2194624F6 (THYRTUT03), 2212407F6 (SINTFET03), 2708944F6 (PONSAZT01), 2708944H1 (PONSAZT01), 4895659H1 (LIVRTUT12)
15	67	3315012	293TF1T01	532568R6 (BRAINOT03), 1300242F1 (BRSTNOT07), 1329265F1 (PANCNOT07), 1439786H1 (PANCNOT08), 2327916X23C1 (COLNNOT11), 2381037X37C1 (ISLTNOT01), 2381037X39C1 (ISLTNOT01), 3315012H1 (293TF1T01), SAEB00241R1
16	68	4155412	ADRENOT14	555524R6 (SCORNOT01), 4155412F6 (ADRENOT14), 4155412H1 (ADRENOT14), 4943387F6 (BRAIFEN05)

Table 1 (cont.)

Polypeptide SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
17	69	4831840	BRAVTXT03	286660H1 (EOSIHET02), 422026H1 (CARCTXT01), 1734445F6 (COLNNOT22), 1734445T6 (COLNNOT22), 1970421F6 (UCMCL5T01), 2512308H1 (CONUTUT01), 4831840H1 (BRAVTXT03)
18	70	5676581	293TF2T01	702633R6 (SYNORAT03), 1000026R1 (BRSTNOT03), 2631308F6 (COLNTUT15), 3012653H1 (MUSCNOT07), 3252744H1 (OVARTUN01), 3315168H2 (293TF2T01), 3530354H1 (BLADNOT09), 4289137H1 (BRABDIR01), 4974749H1 (HELATXT03), 5676581H1 (293TF2T01)
19	71	034159	THP1NOB01	034159H1 (THP1NOB01), 034159X305D3 (THP1NOB01), 406358R6 (EOSIHET02), 1974550F6 (UCMCL5T01), 3471911H1 (LUNGNOT27), 3522363H1 (ESOGTUN01), 4326520H1 (TLYMUNT01), SCJA01020V1, SCIA01764V1
20	72	129023	TESTNOT01	129023R6 (TESTNOT01), 775480R1 (COLNNOT05), 1649938F6 (PROSTUT09), 2518140F6 (BRAITUT21), 2688123H1 (LUNGNOT23), 4306520H1 (MONOTXT01)
21	73	1358940	LUNGNOT09	879273R1 (THYRNOT02), 967670T1 (BRSTNOT05), 1358940F6 (LUNGNOT09), 1358940H1 (LUNGNOT09), 1809259H1 (PROSTUT12), 1818790F6 (PROSNOT20), 1886716F6 (BLADTUT07), 1905126F6 (OVARNOT07), 3508881H1 (CONCNOT01), 3687018F6 (HEAANOT01), 3812474F6 (TONSNOT03)
22	74	1682320	PROSNOT15	1214001T1 (BRSTTUT01), 1259957F1 (MENITUT03), 1375132H1 (LUNGNOT10), 1682320H1 (PROSNOT15), 3137047H1 (SMCCNOT01), 3805984H1 (BLADTUT03), 3806302H1 (BLADTUT03)
23	75	1728263	PROSNOT14	1269315H1 (BRAINOT09), 1453910F1 (PENITUT01), 1728263H1 (PROSNOT14), g2115530
24	76	1867626	SKINBIT01	667711T6 (SCORNOT01), SXYA01116V1, SXYA01833V1, SXYA02442V1

Table 1 (cont.)

25	77	1990126	CORPNOT02	426763T6 (BLADNOT01), 1647316F6 (PROSTUT09), 1757430R6 (PITUNOT03), 1830621F6 (THP1AZT01), 1990126H1 (CORPNOT02), 3250740H1 (SEMVNOT03)
26	78	2104180	BRAITUT02	1350750F1 (LATRTUT02), 1502445F1 (BRAITUT07), 1519125X301D1 (BLADTUT04), 2104180H1 (BRAITUT02), 2733677H1 (OVARTUT04)
27	79	2122241	BRSTNOT07	1402761H1 (LATRTUT02), 1402761T6 (LATRTUT02), 2122241F6 (BRSTNOT07), 2122241H1 (BRSTNOT07), 4989861H1 (LIVRTUT11)
28	80	2580428	KIDNTUT13	157262F1 (THP1PLB02), 1914234X29C1 (PROSTUT04), 1914467X12C1 (PROSTUT04), 1914467X13C1 (PROSTUT04), 1915166X14C1 (PROSTUT04), 2580428H1 (KIDNTUT13), SBKA01222F1
29	81	3397189	UTRSNOT16	759108R6 (BRAITUT02), 1911587T6 (CONNTUT01), 3397189H1 (UTRSNOT16)
30	82	4881249	UTRMTMT01	080470R1 (SYNORAB01), 998242R6 (KIDNTUT01), 4549519H1 (HELAUNT01), 4881249H1 (UTRMTMT01), SXAE01512V1, SXAE02289V1, SXAE00433V1
31	83	431871	EOSINOT03	431871H1 (BRAVUNT02), 460185R1 (KERANOT01), 636514F1 (NEUTGMT01), 1975990T6 (PANCTUT02), 2212046H1 (SINTFET03), 2257310R6 (OVARTUT01), 2300180R6 (BRSTNOT05), 4884920F6 (LUNLTMT01), SCEA00887V1
32	84	526155	EOSINOT02	526155H1 (EOSINOT02), 794168R6 (OVARNOT03), 1260927R1 (SYNORAT05), 1975556F6 (PANCTUT02), 5157385H1 (BRSTTMT02)
33	85	676234	CRBLNOT01	676234H1 (CRBLNOT01), 2241232F6 (PANCTUT02), 2241232T6 (PANCTUT02), 2824092H1 (ADRETUT06), 4248435T6 (BRABDIT01)
34	86	720145	SYNOOAT01	433978H1 (THYRNOT01), 720145H1 (SYNOOAT01), 720145R6 (SYNOOAT01), 2107540T6 (BRAITUT03), 4722278H1 (COLCTUT02)
35	87	1001951	BRSTNOT03	1001951H1 (BRSTNOT03), 1001951R6 (BRSTNOT03), SXYA00708V1, SXYA01879V1, SXYA00520V1, SXYA00731V1, SXYA00926V1
36	88	1243349	LUNGNOT03	050083X316F1 (CHAONOT01), 050083X326F1 (CHAONOT01), 050083X346F1 (CHAONOT01), 050083X350F1 (CHAONOT01), 1243349H1 (LUNGNOT03), 2751089R6 (THP1AZS08), 3773254F6 (BRSTNOT25), 3997530H1 (PROSBPS05), g844357, g1940784, g4539083

Table 1 (cont.)

37	89	1338201	COLNNOT13	256461H1 (HNT2RAT01), 1338201H1 (COLNNOT13), 1338201X12 (COLNNOT13), 1338201X18 (COLNNOT13), 1338201X21 (COLNNOT13), 20781Z7H1 (TSLTNOT01), g777838_g1146680, g1406379
38	90	1405141	LATRTUT02	189682R6 (CARDNOT01), 551762R6 (SCORNOT01), 1405141X302D1 (LATRTUT02), 1459886X16C1 (COLNFET02), 2604416H1 (UTRSNOT10), 2836108H2 (TLYMNOT03), 3031895F6 (TLYMNOT05), 3127628H1 (LUNGTUT12), 3402733H1 (ESOGNOT03), 4289784F6 (BRAEDIR01), 4339406H1 (BRAUNOT02), 4712515H1 (BRAIHCT01), 4746879H2 (SMCRUNT01), 5091792F6 (UTRSTMR01), 5679882H1 (BRAENOT02), 5927661H1 (BRAIFET02)
39	91	1686305	PROSNOT15	4991154R6 (NEUTLPT01), 1686305F6 (PROSNOT15), 1686305H1 (PROSNOT15), 2306450R6 (NGANNOT01), 2446232F6 (THP1NOT03), 2446232H2 (THP1NOT03), 3050482H1 (LUNGNOT25), 3694303F6 (LUNGNOT35), 3825239H1 (BRAIHCT01), 3931022H1 (PROSTUT09), 4383527H1 (BRAIWHT02)
40	92	1688972	PROSTUT10	878019H1 (LUNGAST01), 1255436F2 (MENITUT03), 1330287F1 (PANCNOT07), 1400664F6 (BRAITUT08), 1688972H1 (PROSTUT10), 2018742F6 (THP1NOT01), 2047754X12F1 (SININOT01), 3002925H1 (TLYMNOT06), 3744192H1 (THYMNOT08)
41	93	1812494	PROSTUT12	1322590F6 (BLADNOT04), 1684555F6 (PROSNOT15), 2120930H1 (BRSTNOT07), 2266093H1 (UTRSNOT02), 2631470F6 (COLNTUT15), 3980110H1 (LUNGTUT08), 5115462H1 (ENDITXT01), SADA00912R1
42	94	2013853	TESTNOT03	2013853H1 (TESTNOT03), SKBC01227V1, SCGA04222V1
43	95	2284925	BRAINON01	464655X11 (LATRNOT01), 464655X12 (LATRNOT01), 464655X28 (LATRNOT01), 482019X21 (HNT2RAT01), 1443611R1 (THYRNOT03), 1443611X22 (THYRNOT03), 2284925H1 (BRAINON01), 2882173F6 (UTRSTUT05), 3485205F6 (KIDNNOT31), 3485205T6 (KIDNNOT31), SAABO0144R1

Table 1 (cont.)

44	96	2376728	ISLTNOT01	413593R6 (BRSTNOT01), 823803R1 (PROSNOT06), 860037R1 (BRAITUT03), 1282102F1 (COLANOT16), 1733518F6 (BRSTTUT08), 2376728F6 (ISLTNOT01), 2376728H1 (ISLTNOT02), 2937285F6 (THYMFET02), 3108296H1 (BRSTTUT15), 3212546H1 (BLADNOT08), 3462704H1 (293TF2T01)
45	97	2790762	COLNTUT16	126628F1 (LUNGNOT01), 126628R1 (LUNGNOT01), 2790762F6 (COLNTUT16), 2790762H1 (COLNTUT16), 4002872H1 (HNT2AZS07), g6787055
46	98	2869164	THYRNOT10	1607765F6 (LUNGNOT15), 2869164F6 (THYRNOT10), 2869164H1 (THYRNOT10), 2869164T6 (THYRNOT10), 2890205H1 (LUNGFET04), 2891521F6 (LUNGFET04), 3094580X305D1 (CERVNOT03)
47	99	3317629	PROSBPT03	3166243H1 (SAMABT007), 3317629F6 (PROSBPT03), 3421114X302F1 (UCMCNOT04), 4635773F6 (NYEPTXT01), 4635773T6 (NYEPTXT01)
48	100	3870488	BMARNOT03	1670688F6 (BMARNOT03), 3039406T6 (BRSTNOT16), 3870488H1 (BMARNOT03), 4773630H1 (BRAQNOT01)
49	101	3886318	UTRSNOT05	1981820F1 (KIDNNOT02), 4747111R1 (MMLRIDT01), 7332277R1 (LUNGNOT03), 1236870F1 (LUNGFET03), 1502818F1 (BRAITUT07), 3742588H1 (THYMNOT08)
50	102	4043934	LUNGNOT35	4043934F6 (LUNGNOT35), 4043934H1 (LUNGNOT35), g1664159, g2114678, g3665589
51	103	4371445	THYMNOT11	4371445F6 (THYMNOT11), 4371445H1 (THYMNOT11), 4371445T6 (THYMNOT11), g691417
52	104	5527925	KIDNNOT34	878842R1 (THYRNOT02), 1662614F6 (BRSTNOT09), 1820183F6 (GBLATUT01), 2275208H1 (PROSNON01), 2864564H1 (KIDNNOT20), 2890511H1 (LUNGFET04), 4312193H1 (BRAFNOT01), 5175111F6 (EPIBTXT01), 5876074H1 (BRAUNOT01)

Table 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences and Motifs	Homologous Sequences	Analytical Methods and Databases
1	446	T24 T144 S251 S384 S404 T114 T118 T121 T172 S181 S247 Y53 Y422	N117 N232	SH3 domain: E387-I441	g2232009, thyroid hormone responsive protein [Rattus norvegicus]. Shah, G.N. et al. (1997) Biochem. J. 327:617-23.	BLAST - GenBank BLAST - DOMO BLIMPS - BLOCKS BLIMPS - PRINTS HMMER - PFAM MOTIFS
2	340	T26 S51 T146 S211 S270 S308 S73 S277 S317 Y71		SH2 domain: W240-Y316	g3738265 SH2 domain-containing protein [Mus musculus]	BLAST - GenBank BLAST - DOMO BLIMPS - PRINTS HMMER - PFAM MOTIFS
3	353	T45 S232 T353 T78 S88 S163 S176 T222 S240 S284 S302 T326 S338 S116 S120 T154 S226 S295 S337		Pleckstrin homology domains: T247-T353 G4-H104 S120-K250	g5381422 pleckstrin 2 [Homo sapiens]	BLAST - GenBank BLAST - PRODOM HMMER - PFAM MOTIFS
4	593	S230 S415 T84 T115 S214 S231 S309 S355 S372 T377 T387 S529 S580 S5 T36 S41 S90 S205 T263 S264 T343 T371 S410 S445 S483 S528 T547	N19 N542	SH3 domain: L453-L507 EPS8 region - SH3/phosphorylation domain: S2-P395	g3093217 Eps8 (EGF receptor kinase substrate) [Mus musculus]	BLAST - GenBank BLAST - PRODOM HMMER - PFAM MOTIFS

Table 2

5	358	T42 S82 T204 T233 S261 T271 T279 S285 S330 S55 T102 S153 S254 S353	N338	Ankyrin repeat: G40-G67	g485107 similar to ankyrin repeat region [C. elegans]	BLAST - GenBank HMMER - PFAM MOTIFS
6	749	S137 T401 S406 T407 S580 T29 S140 S148 S149 S287 T336 S342 S360 S511 S551 T627 T29 S104 T368 S480 T616 Y141 Y303	N147 N392 N453 N640	Transmembrane domain: W280-I297 SH3 domain: R483-L537 Probable rabGAP domains: I159-P168 Y200-G205	g1519685 contains similarity to SH3 domains [C. elegans].	BLAST - GenBank BLIMPS - PRINTS BLIMPS - PFAM HMMER - PFAM HMMER MOTIFS
7	139	T51 T113 S106	N31		g169306 calmodulin [Phytophthora infestans]	BLAST - GenBank
8	539	S52 S84 T114 S186 S430 T468 S15 S110 S241 S307 S309 S353 S362 S363 S389 S485 S118 S169 S181 S210 T319 S385 T434 T523 Y208 Y305	N533	Pleckstrin homology domain: R192-A291	g4151807 membrane-associated guanylate kinase-interacting protein 2 (Maguin-2) [Rattus norvegicus]	BLAST - GenBank HMMER - PFAM MOTIFS
9	319	S169 S214 S233 S240 S150	N126	Tumor necrosis factor and nerve growth factor receptors - Conserved domain containing six cysteines: L166-C204	g2809400 Sprouty 2 (antagonist of FGF signaling) [Homo sapiens]	BLAST - GenBank HMMER - PFAM MOTIFS

Table 2 (cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences and Motifs	Homologous Sequences	Analytical Methods and Databases
10	747	T194 T344 T561 S655 S45 T58 T60 T74 T81 T171 S287 T294 S446 T526 S608 T610 T733 S126 S133 T165 S170 T190 S234 T251 T429 S470 S492 T522 S546 S735 S741 Y504 Y543	N32 N54 N533 N642		g550420 trg (transcript negatively regulated by thyroid stimulating hormone) [Rattus norvegicus]	
11	266	S62 T76 T183 S222 S4 T5 S256 S260 Y179	N47	Diacylglycerol/phorbol ester binding domain: E177-N223		PROFILESCAN HMMER - PFAM MOTIFS
12	345	T87 S131 S213 T241 S299 S323 T34 T69 T223 S307	N40 N70	Annexin domain: G58-L110 L122-R143 I137-L182 L262-F316 E311-D326 A327-C340	**g3688370, annexin 31 (annexin XXXI) [Homo sapiens]. Morgan, R.O. and Fernandez, M.P. (1998) FEBS Lett. 434:300-304.**	BLAST - GenBank HMMER - PFAM BLIMPS - BLOCKS BLIMPS - PRINTS MOTIFS
13	437	S40 T66 T79 S93 T241 T289 S305 S342 T375 S47 S270 S362 T371 T393			g685183 NGD5 gene product (regulated by opioid treatment) [Murinae gen. sp.]	BLAST - GenBank MOTIFS

Table 2 (cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences and Motifs	Homologous Sequences	Analytical Methods and Databases
14	441	S333 S419 T10 T24 T322 S403. S407 S422 T453 S33 S270 S329 T352 S487		Ankyrin repeats: G46-N73 G80-D107	g6460678 ankyrin-related protein [Deinococcus radiodurans].	BLAST - GenBank HMMER - PFAM MOTIFS
15	487	S31 T51 S62 T220 T237 T254 T427 S453 T471 S482 T483 T95 S182	N242 N481	Signal peptide: M1-A28 Histidine acid phosphatase domains: R88-T95 K311-W323 Acid phosphatase-like region: E75-S484	g4105496 multiple inositol polyphosphate phosphatase [Mus musculus].	BLAST - GenBank BLAST - PRODOM BLIMPS - BLOCKS HMMER SPSCAN MOTIFS
16	282	S25 T125 T157 T203 S31 S46 S107 S133 S194 S218 S257	N17 N74 N216		g688297 VDUP1 (1,25-dihydroxy-vitamin D-3 up-regulated polypeptide [Homo sapiens].	BLAST - GenBank MOTIFS
17	581	T147 T327 S477 S41 T119 T123 T129 T209 S232 S243 S257 S299 S341 S347 T366 S371 S142 S220 S223 S237 S276 S323 S399 T472 T487 S518	N221 N358		**g6013191, activating signal cointegrator 1 [H. sapiens]. Kim, H.J.et al. (1999) Mol. Cell. Biol. 19:6323-6332.**	BLAST - GenBank MOTIFS

Table 2 (cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences and Motifs	Homologous Sequences	Analytical Methods and Databases
18	530	S23 T46 S219 S221 T267 T268 S290 S303 T370 T382 S406 S446 T2 S31 S195 S339 S358 T375 S379 S399 T424 T445 T504	N43 N99	Signal peptide: M1-S23 WW/rsp5/WWP repeat domain: E123-P153 Trehalase domains: P80-T90 E129-N142	gi1255031 FBP 30 (formin binding protein 30) [Mus musculus]	BLAST - GenBank SPSCAN HMMER - PFAM BLIMPS - BLOCKS MOTIFS
19 (O34159)	475	S264 T5 T9 S33 S163 S171 S211 S217 S241 T267 S343 S370 T386 S472 S16 S110 S111 S151 S152 S246 T260 S264 T405	N15 N62 N101 N291 N384 N443	Pleckstrin M79-D189 GTPase activator K248-A459	g35013 n-chimaerin	Motifs BLAST_GENBANK HMMER_PFAM BLIMPS_PRINTS BLIMPS_PFAM BLAST_PRODOM BLAST_DOMO
20 (1290023)	368	S8 S54 S70 S99 T158 S159 S253 S361 S30 T152 S308	N24 N68 N359	Signal peptide: M1-Q25 WW (signal transduction associated) domain: Y61-P75		Motifs SPSCAN BLIMPS_PRINTS
21 (1358940)	476	S104 S182 T343 S122 T148 T157 T197 S205 T360 S429 T467 T133 T269 T292 T323 S339		EF-hand Calcium binding domain: D231-D421	g3297882 atopy-related autoantigen CALC [H. sapiens].	Motifs BLAST_GENBANK HMMER_PFAM BLAST_PRODOM

Table 2 (cont.)

22 (1682320)	171	T70 T151 S97 Y11 Y24		Leucine zipper: L38-L59 Peptidyl-Prolyl Cis-Trans Isomerase CYP6: L59-F170	g1354207 rof1 FK506 binding protein	Motifs BLAST_GENBANK BLAST_PRODOM BLAST_DOMO
23 (1728263)	163	S16 S39 S56 T101 T112 T131 S148 Y92	N70	EF-hand calcium binding domain: D140-F152	g21209 caltractin **[Scherffelia dubia]**	Motifs BLAST_GENBANK BLAST_PRODOM
24 (1867626)	354	T230 T148 T252 S306 S315 T328 S8 T20 T27 S40 S71 T189 T244 T259 T288	N58 N64 N146 N250	Leucine zipper: L326-L347 ATP-Binding motif: E93-E320 Vasodilator-Stimulated Actin-Binding Phosphoprotein motif: M1-A109	g3834607 homer-1b [Mus musculus]	Motifs BLAST_GENBANK BLAST_PRODOM
25 (1990126)	365	T36 S47 S191 T198 S200 T359 T56 T124 S307 Y80 Y155	N189 N264 N297 N320	Src homology domain 3: R308-L364	g1407657 endophilin II	Motifs BLAST_GENBANK HMMER_PFAM BLIMPS_PRINTS BLAST_DOMO
26 (2104180)	274	T71 S126 T137 S230 S251 T7 S141 S155 Y152	N56	Protein Kinase C2 domain: L55-H135	g3876326 similar to protein kinase C2	Motifs BLAST_GENBANK HMMER_PFAM
27 (2122241)	129	T11 S24 S58 T100 S112 T89		Nascent polypeptide-associated complex alpha chain: G39-T128		Motifs BLAST_DOMO
28 (2580428)	626	S84 S93 S192 S278 T411 S10 S18 T114 S302 S482	N293 N577 N599	Interferon-gamma inducible protein motif: M1-M115, C522-A574	**g4886493 and g6942315, [H. sapiens].**	Motifs BLAST_PRODOM

Table 2 (cont.)

29 (3397189)	157	S7	N97	Signal peptide: M1-S29 Glycosyl hydrolase: L62-L137 Beta D Galactosidase: R28-L153	g2547317 lysosomal beta-galactosidase **WO9914328**	Motifs BLAST_GENBANK SPSCAN HMMER BLIMPS_BLOCKS BLAST_PRODOM
30 (4881249)	383	T7 T26 S90 T62 T81 S102 T363 S3 T210 T256 T286 Y158	N70 N190 N223 N289	WWP (Signal transduction associated proline binding domain):L201-P230	g5059333 ubiquitin ligase	Motifs BLAST_GENBANK HMMER_PFAM BLIMPS_PRINTS
31	478	S186 S202 S270 S354 S455 S9 S94 T175		Signal peptide: M1-A64 Ankyrin repeat: D36-E63 Ankyrin repeat protein domain: Q111-Y174; C285-V447	**g1204166, hypothetical Ank-repeat/BTB-domain protein [Schizosaccharomyces pombe].**	MOTIFS SPSCAN HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS BLAST-PRODOM
32	275	S259 T74 T173 S186 T231 S21 T63 T219 S255 S267			COP9 complex subunit 7b [Mus musculus] g3309176	BLAST-Genbank MOTIFS
33	217	T4 T106 S209		Signal peptide: M1-C25 Transmembrane domains: A82-T100; R116-I34 Claudin signature: T21-W30; G49-V55 Q63-L73; D146-V152	claudin-9 protein [Mus musculus] g4325296	BLAST-Genbank MOTIFS SPSCAN HMMER BLIMPS-PRINTS

Table 2 (cont.)

34	74	S6 T58 S54		TPR domain: Y18-P46			MOTIFS HMMER-PFAM BLIMPS-PRODOM
35	367	S309 S24	N240	Transmembrane domain: L257-T277 Armadillo/beta-catenin repeat: 219-252; L252-L265			MOTIFS HMMER BLIMPS-PFAM
36	1113	T17 S43 S609 T755 T52 T215 S239 S287 T307 T313 S504 S510 S535 T536 S635 S688 S804 S812 T856 S863 T884 S938 T983 S996 S1004 S5 T196 S353 S433 T550 S592 S593 S727 T748 S762 S839 T928 S944 T952 T968 S1074 Y23 Y134	N175 N323 N365 N633 N724	PDZ domains: V53-E135; E152-D237 L252-H335; E472-D560 H573-D657; T673-Q754 K989-N1070 SH3 domain repeat: G98-K111 SH3 domain protein signature: V153-G249 GLGF domain: L676-K752	AMPA receptor interacting protein GRIP [Rattus norvegicus] g1890856		BLAST-Genbank MOTIFS HMMER-PFAM BLIMPS-PFAM BLIMPS-PRODOM BLAST-PRODOM BLAST-DOMO
37	511	S147 S88 S136 T228 T320 S467 T15 T81 T118 T168 S281 S289 S311 S354 S455 T461 T480 T494 Y16 Y114	N86 N116 N315 N316 N355 N403 N425 N429 N478	SH3 domain: Q342-L400	g6563258, insulin receptor tyrosine kinase substrate [Homo sapiens].		BLAST-Genbank MOTIFS HMMER-PFAM

Table 2 (cont.)

38	1177	S421 T936 T96 T121 S164 S209 T256 S277 S325 S374 S388 T397 S435 S443 T456 T519 S662 T669 S727 T901 S983 S1114 S14 T70 S307 S331 S416 S545 T565 S609 T626 T703 S804 S845 S853 S867 T921 S972 T1021 S1108 Y214 Y879 Y171	N84 N1112	Armadillo beta-catenin repeat: I196-L205	trg [Rattus norvegicus] g550420	BLAST-Genbank MOTIFS BLIMPS-PFAM
39	665	S245 T358 S480 T76 S110 S119 S121 T266 S284 S481 S521 S561 S632 S654 S655 S72 S73 S130 T171 S205 T411 S428 T475 S476 T491 S513 S523 T634 Y165 Y567 Y578	N197 N479	TPR domains: L136-P164; Y204-P232 E285-G313; P319-G347 F353-P381 TPR repeat: K137-E252; K286-K395	**g6272680, TPR-containing protein involved in spermatogenesis TPIS [Mus musculus]. Takaishi, M. and Huh, N.H. (1999) Biochem. Biophys. Res. Commun. 264:81-85.**	BLAST-Genbank MOTIFS HMMER-PFAM BLIMPS-PRODOM BLAST-DOMO
40	125	T119 T67		Signal peptide: M1-A53 SH3 domain: R68-L124 R68-A78; K112-L124		MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS

Table 2 (cont.)

Poly-peptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
41	366	S43 S45 T102 S157 T202 T220 S293 S219 T256 T325 S350 Y237		Signal peptide: M1-S30 Ankyrin repeat: G174-S206	**g289693, homology with isopentenyl-diphosphate-delta-isomerase; [C. elegans]. Sulston, J. et al. (1992) Nature 356:37-41.**	MOTIFS SPSCAN HMMER-PFAM BLIMPS-PFAM
42	173	S16 S42 S48 T67 S100 S111 S152 S86	N126	EF Hands: E22-R53; L57-F85 K94-M122; L135-L163 S-100/IcaBP type calcium binding protein signature: L6-E57; L132-K168 Recoverin family signature: V61-T82; S86-D105 Calmodulin repeat: R25-I79; L119-S157	calcineurin B-like protein (CBLP) [Rattus norvegicus] g220688	BLAST-GenBank MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS PROFILESCAN BLAST-DOMO
43	761	S227 S293 S393 S19 S43 T149 T161 S277 T346 T370 T415 T529 T572 S630 T683 S711 T746 S74 S196 S252 S283 S300 T444 T472 T591 S754 Y589	N117 N467 N492 N555	3'5'-cyclic nucleotide phosphodiesterase domain: Y490-H729 D418-W744 3'5'-cyclic nucleotide phosphodiesterase signature: L2-H56; L449-H485 Y490-H501; L516-D556 T572-E610; D657-S711	CAMP-specific cyclic nucleotide phosphodiesterase PDE8 [Mus musculus].	BLAST-GenBank MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS PROFILESCAN BLAST-PRODOM BLAST-DOMO

Table 2 (cont.)

Poly-peptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
44	249	S16 S89 T115 S212 S239 T12 T117 S137 S187 S197 S230 Y208	N84	Pleckstrin homology domain: V35-T131 Rho-GEF domain: L36-C178; E118-D245 FYVE zinc finger: N59-Y64; R171-C183 R202-S212	**g3292902, PUTATIVE RHO/RAC GUANINE NUCLEOTIDE EXCHANGE FACTOR [H. sapiens].**	BLAST-GenBank MOTIFS HMMER-PFAM BLIMPS-PFAM BLAST-PRODOM
45	247	S109 S44 S53 S123 T138 S167 S95 T98 S127 T220	N90		putative phosphatidyl-inositol 3-kinase [Carassius auratus] g4001815	BLAST-GenBank MOTIFS
46	316	S313 S201 T223 T262 Y186 Y270			g3811347, cytosolic phospholipase A2 beta [Homo sapiens].	BLAST-GenBank MOTIFS
47	334	T119 S97 T182 T244 S316 S317 S324 S60 T72 S97 T179 S187 S290 Y52 Y323	N58 N322	Fes/CIP4 homology domain: G8-L98 SH3 domain/division control protein signature: F6-F287	macrophage actin-associated-tyrosine-phosphorylated protein [Mus musculus] g3947712	BLAST-GenBank MOTIFS HMMER-PFAM BLAST-PRODOM
48	113	T65 S66 T43		SH3 domain: K34-L90	SLP-76 associated protein (TCR-stimulated PK substrate) [Homo sapiens] g2072873	BLAST-GenBank MOTIFS HMMER-PFAM BLIMPS-PRINTS

Table 2 (cont.)

Poly-peptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
49	264	S18 T76 T163 S181 S167 S223		Wilm's tumor protein signature: D97-P111	SH3 domain binding protein [Rattus norvegicus] g1185397 (P-value= 4.6x10-8).	BLAST-GenBank MOTIFS BLIMPS-PRINTS
50	185	T24 S81 S149 S151 S160 S162 S75 S99 S177 Y176		EF-hands: K101-L129; L143-S171 Recoverin family signature: I23-G42; S93-N112 Calcium binding protein signature: E12-Y104	g1848271, Calcium and integrin binding protein CIB [Homo sapiens]	BLAST-GenBank MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS BLAST-PRODOM
51	72	T18 S25 T20		Synapse-associated SH3 domain protein signature: M13-E67	homolog of Drosophila discs large protein isoform 1 [Homo sapiens] g558438 (P-value= 7.9x10-9).	BLAST-GenBank MOTIFS BLAST-PRODOM
52	434	S123 T128 S418 S94 T105 S159 S205 T291 S308 S314 T326 T358 S383 S406 S84 T128 T212 Y220	N216 N231	Signal peptide: M1-A50 EF hand: I366-R394 Recoverin family signature: V370-L391	similar to EF hand [C. elegans] g3875264.	BLAST-GenBank MOTIFS SPSCAN HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS

Table 3

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
53	543-587	Reproductive (0.211) Developmental (0.158) Nervous (0.158)	Cancer (0.421) Cell Proliferation (0.263) Inflammation (0.211)	PBLUESCRIPT
54	273-317 651-695	Nervous (0.462) Gastrointestinal (0.385) Cardiovascular (0.077) Developmental (0.077)	Cancer (0.538) Cell Proliferation (0.308) Inflammation (0.154)	PSPORT1
55	110-154	Developmental (0.174) Gastrointestinal (0.174) Reproductive (0.174)	Cell Proliferation (0.435) Cancer (0.261) Inflammation (0.174)	pINCY
56	273-317 1461-1505	Gastrointestinal (0.821) Reproductive (0.143) Developmental (0.036)	Cancer (0.607) Inflammation (0.286) Cell Proliferation (0.036)	pINCY
57	595-639	Reproductive (0.313) Nervous (0.217) Hematopoietic/Immune (0.120)	Cancer (0.482) Inflammation (0.217) Cell Proliferation (0.169)	pINCY
58	703-747 1297-1341	Reproductive (0.250) Nervous (0.205) Gastrointestinal (0.125)	Cancer (0.509) Cell Proliferation (0.196) Inflammation (0.196)	pINCY
59	417-461	Nervous (0.300) Cardiovascular (0.200) Reproductive (0.200)	Inflammation (0.300) Trauma (0.300) Cancer (0.200) Cell Proliferation (0.200)	pINCY
60	1189-1233	Nervous (1.000)	Neurological (0.500) Trauma (0.333)	PSPORT1
61	272-316	Reproductive (0.314) Gastrointestinal (0.186) Nervous (0.157)	Cancer (0.529) Inflammation (0.200) Cell Proliferation (0.129)	PSPORT1
62	273-317 2055-2099	Hematopoietic/Immune (0.333) Reproductive (0.238) Gastrointestinal (0.167)	Inflammation (0.452) Cancer (0.333) Trauma (0.143)	PSPORT1
63	1-34	Reproductive (0.256) Nervous (0.188) Gastrointestinal (0.120)	Cancer (0.504) Inflammation (0.203) Cell Proliferation (0.195)	PSPORT1

Table 3 (cont.)

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
64	489-533	Reproductive (0.312) Gastrointestinal (0.125) Nervous (0.125)	Cancer (0.438) Cell Proliferation (0.375) Inflammation (0.188)	pINCY
65	273-317	Reproductive (0.265) Nervous (0.224) Developmental (0.102)	Cancer (0.469) Cell Proliferation (0.286) Inflammation (0.204)	pINCY
66	1028-1072	Cardiovascular (0.286) Nervous (0.200) Reproductive (0.200)	Cancer (0.429) Cell Proliferation (0.171) Inflammation (0.171)	pINCY
67	325-369	Reproductive (0.222) Nervous (0.194) Cardiovascular (0.167) Gastrointestinal (0.167)	Cancer (0.472) Cell Proliferation (0.333) Inflammation (0.139)	pINCY
68	921-965	Endocrine (0.250) Musculoskeletal (0.250) Reproductive (0.250) Urologic (0.250)	Cancer (0.750) Trauma (0.250)	pINCY
69	1029-1073	Reproductive (0.216) Gastrointestinal (0.176) Hematopoietic/Immune (0.157)	Cancer (0.510) Inflammation (0.275) Cell Proliferation (0.118)	pINCY
70	1405-1449	Hematopoietic/Immune (0.200) Nervous (0.200) Gastrointestinal (0.160) Reproductive (0.160)	Cancer (0.360) Inflammation (0.360) Cell Proliferation (0.200)	pINCY
71	280-324	Hematopoietic/Immune (0.500) Gastrointestinal (0.092) Reproductive (0.092)	Cancer (0.364) Inflammation (0.295) Cell proliferation (0.205)	pBLUESCRIPT
72	380-424	Reproductive (0.227) Gastrointestinal (0.205) Cardiovascular (0.114)	Cancer (0.455) Inflammation (0.364) Trauma (0.045)	pBLUESCRIPT

Table 3 (cont.)

73	433-477	Nervous (0.241) Reproductive (0.231) Gastrointestinal (0.130)	Cancer (0.398) Inflammation (0.333)	pINCY
74	786-830	Reproductive (0.342) Nervous (0.210)	Cancer (0.474) Cell proliferation (0.184) Inflammation (0.105)	pINCY
75	1-47	Gastrointestinal (0.286) Reproductive (0.286) Developmental (0.143) Hematopoietic/Immune (0.143)	Cancer (0.571) Cell proliferation (0.286) Inflammation (0.143)	pINCY
76	380-424	Nervous (0.300) Reproductive (0.200)	Inflammation (0.400) Cancer (0.200) Cell proliferation (0.200)	pINCY
77	30-74	Gastrointestinal (0.222) Reproductive (0.222) Cardiovascular (0.153) Nervous (0.153)	Inflammation (0.375) Cancer (0.361) Cell proliferation (0.139)	pINCY
78	487-531	Nervous (0.300) Reproductive (0.183) Cardiovascular (0.117)	Cancer (0.433) Inflammation (0.200) Neurological (0.133)	pSPORT1
79	595-639	Reproductive (0.305) Nervous (0.179) Gastrointestinal (0.126)	Cancer (0.526) Inflammation (0.326) Cell proliferation (0.179)	pINCY
80	109-153	Reproductive (0.235) Hematopoietic/Immune (0.216) Nervous (0.157)	Cancer (0.529) Inflammation (0.255)	pINCY
81	109-153	Gastrointestinal (0.286) Musculoskeletal (0.286) Reproductive (0.286)	Cancer (0.571) Inflammation (0.286)	pINCY
82	163-207	Reproductive (0.424) Gastrointestinal (0.152) Nervous (0.121)	Cancer (0.424) Inflammation (0.242) Cell proliferation (0.182)	pINCY
83	496-540	Reproductive (0.242) Nervous (0.182) Hematopoietic/Immune (0.167)	Cancer (0.455) Inflammation/Trauma (0.364) Cell Proliferation (0.152)	PSPORT1
84	1022-1066	Reproductive (0.248) Nervous (0.208) Cardiovascular (0.136)	Cancer (0.464) Inflammation/Trauma (0.304) Cell Proliferation (0.184)	PSPORT1

Table 3 (cont.)

85	39-83	Nervous (0.286) Endocrine (0.143) Gastrointestinal (0.143) Hematopoietic/Immune (0.143) Reproductive (0.143)	Cancer (0.571) Inflammation/Trauma (0.286) Neurological (0.143)	PSPORT1
86	471-515	Hematopoietic/Immune (0.167) Musculoskeletal (0.167) Reproductive (0.167)	Cancer (0.556) Cell Proliferation (0.167) Inflammation/Trauma (0.167)	PSPORT1
87	595-639 982-1026	Reproductive (0.294) Cardiovascular (0.176) Gastrointestinal (0.176)	Cancer (0.706) Inflammation/Trauma (0.294) Cell Proliferation (0.118)	PSPORT1
88	1101-1163	Reproductive (0.625) Gastrointestinal (0.250) Cardiovascular (0.125)	Cancer (0.750) Inflammation/Trauma (0.250)	PSPORT1
89	1245-1289	Gastrointestinal (0.387) Reproductive (0.355) Cardiovascular (0.065)	Cancer (0.548) Inflammation/Trauma (0.323) Cell Proliferation (0.161)	pINCY
90	3720-3764	Nervous (0.328) Gastrointestinal (0.121) Reproductive (0.121)	Cancer (0.397) Inflammation/Trauma (0.310) Cell Proliferation (0.155)	pINCY
91	659-703 1622-1666	Hematopoietic/Immune (0.273) Nervous (0.182) Cardiovascular (0.121) Reproductive (0.121)	Cancer (0.455) Cell Proliferation (0.333) Inflammation/Trauma (0.303)	pINCY
92	104-148	Reproductive (0.310) Nervous (0.241) Developmental (0.138) Gastrointestinal (0.138)	Cancer (0.483) Inflammation/Trauma (0.241) Cell Proliferation (0.172)	pINCY
93	820-864	Reproductive (0.340) Cardiovascular (0.120) Nervous (0.120)	Inflammation/Trauma (0.440) Cancer (0.400) Cell Proliferation (0.160)	pINCY
94	504-554	Reproductive (1.000)	Inflammation/Trauma (1.000)	PBLUESCRIPT
95	198-242	Reproductive (0.424) Nervous (0.273)	Cancer (0.576) Inflammation/Trauma (0.182)	PSPORT1
96	307-351 712-756	Reproductive (0.412) Hematopoietic/Immune (0.137) Cardiovascular (0.118) Gastrointestinal (0.118)	Cancer (0.608) Inflammation/Trauma (0.275) Cell Proliferation (0.098)	pINCY

Table 3 (cont.)

97	433-477	Developmental (0.200) Reproductive (0.200) Cardiovascular (0.133) Gastrointestinal (0.133) Nervous (0.133)	Cell Proliferation (0.400) Cancer (0.333) Inflammation/Trauma (0.200)	pINCY
98	474-1018	Cardiovascular (0.190) Reproductive (0.190) Hematopoietic/Immune (0.143) Musculoskeletal (0.143)	Cancer (0.381) Inflammation/Trauma (0.333)	pINCY
99	422-466 998-1042	Hematopoietic/Immune (0.667) Reproductive (0.222) Developmental (0.111)	Inflammation/Trauma (0.556) Cancer (0.222) Cell Proliferation (0.222)	pINCY
100	444-488	Hematopoietic/Immune (0.455) Nervous (0.182) Cardiovascular (0.091)	Inflammation/Trauma (0.546) Cancer (0.182) Cell Proliferation (0.182)	pINCY
101	1578-1622	Reproductive (0.250) Nervous (0.170) Gastrointestinal (0.156)	Cancer (0.482) Inflammation/Trauma (0.345) Cell Proliferation (0.167)	pINCY
102	15-59	Cardiovascular (1.000)	Cancer (1.000)	pINCY
103	487-531	Hematopoietic/Immune (1.000)		pINCY
104	967-1011	Reproductive (0.235) Nervous (0.191) Gastrointestinal (0.147)	Cancer (0.515) Inflammation/Trauma (0.294) Cell Proliferation (0.118)	pINCY

Table 4

Nucleotide SEQ ID NO:	Library	Library Description
53	TESTNOT01	The library was constructed using RNA isolated from the testicular tissue of a 37-year-old Caucasian male, who died from liver disease. Patient history included cirrhosis, jaundice, and liver failure.
54	COLNNOT05	The library was constructed using RNA isolated from the sigmoid colon tissue of a 40-year-old Caucasian male during a partial colectomy. Pathology indicated Crohn's disease involving the proximal colon and including the cecum. The ascending and transverse colon displayed linear ulcerations and skip lesions. Transmural inflammation was present.
55	KIDNNOT09	The library was constructed using RNA isolated from the kidney tissue of a Caucasian male fetus who died at 23 weeks' gestation.
56	COLNFET02	The library was constructed using RNA isolated from the colon tissue of a Caucasian female fetus who died at 20 weeks' gestation.
57	CONNNOT01	The library was constructed using RNA isolated from mesentery fat tissue obtained from a 71-year-old Caucasian male during a partial colectomy and permanent colostomy. Family history included atherosclerotic coronary artery disease, myocardial infarction, and extrinsic asthma.
58	BRAINOT09	The library was constructed using RNA isolated from brain tissue removed from a Caucasian male fetus who died at 23 weeks' gestation.
59	ENDCNOT02	The library was constructed using RNA isolated from dermal microvascular endothelial cells removed from a 30-year-old Caucasian female.
60	HIPONON02	This normalized library was constructed using 1.13 million independent clones from a hippocampus library. RNA was isolated from the hippocampus tissue of a 72-year-old Caucasian female who died from an intracranial bleed. Patient history included nose cancer, hypertension, and arthritis. The normalization and hybridization conditions were adapted from Soares et al. (PNAS (1994) 91:9228).
61	OVARNOT02	The library was constructed using RNA isolated from ovarian tissue removed from a 59-year-old Caucasian female who died of a myocardial infarction. Patient history included cardiomyopathy, coronary artery disease, myocardial infarction, hypercholesterolemia, hypotension, and arthritis.
62	OVARNOT02	The library was constructed using RNA isolated from ovarian tissue removed from a 59-year-old Caucasian female who died of a myocardial infarction. Patient history included cardiomyopathy, coronary artery disease, myocardial infarction, hypercholesterolemia, hypotension, and arthritis.

Table 4 (cont.)

Nucleotide SEQ ID NO:	Library	Library Description
63	ADRETUT01	The library was constructed using RNA isolated from right adrenal tumor tissue removed from a 50-year-old Turkish male during a unilateral adrenalectomy. Pathology indicated a metastatic renal cell carcinoma that formed a circumscribed, spongy, hemorrhagic nodule situated in the region of the medulla. The patient presented with corticoadrenal insufficiency, incisional hernia, and non-alcoholic steato hepatitis. Patient history included renal cell carcinoma. Family history included liver cancer.
64	GBLANOT01	The library was constructed using RNA isolated from diseased gallbladder tissue removed from a 53-year-old Caucasian female during a cholecystectomy. Pathology indicated mild chronic cholecystitis and cholelithiasis with approximately 150 mixed gallstones. Family history included benign hypertension.
65	LUNGTUT09	The library was constructed using RNA isolated from lung tumor tissue removed from a 68-year-old Caucasian male during segmental lung resection. Pathology indicated invasive grade 3 squamous cell carcinoma and a metastatic tumor. Patient history included type II diabetes, thyroid disorder, depressive disorder, hyperlipidemia, esophageal ulcer, and tobacco use.
66	PONSAZT01	The library was constructed using RNA isolated from diseased pons tissue removed from the brain of a 74-year-old Caucasian male who died from Alzheimer's disease.
67	293TFIT01	The library was constructed using RNA isolated from a transformed embryonal cell line (293-EBNA) derived from kidney epithelial tissue. The cells were transformed with adenovirus 5 DNA.
68	ADRENOT14	The library was constructed using RNA isolated from adrenal gland tissue removed from an 8-year-old Black male who died from anoxia.
69	BRAVTXT03	The library was constructed using RNA isolated from treated astrocytes removed from the brain of a female fetus who died at 22 weeks' gestation. The cells were treated with tumor necrosis factor (TNF) alpha and interleukin 1 (IL-1), 10ng/ml each for 24 hours.

Table 4 (cont.)

70	293TF2T01	The library was constructed using RNA isolated from a treated, transformed embryonal cell line (293-EBNA) derived from kidney epithelial tissue. The cells were treated with 5-aza-2'-deoxycytidine and transformed with adenovirus 5 DNA.
71	THP1NOB01	Library was constructed using RNA isolated from cultured, unstimulated THP-1 cells. THP-1 (ATCC TIB 202) is a human promonocyte line derived from the peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia. RNA was isolated from 2x108 cells using GuSCN lysis, followed by DNAse treatment.
72	TESTNOT01	Library was constructed using RNA isolated from the testicular tissue of a 37-year-old Caucasian male, who died from liver disease. Patient history included cirrhosis, jaundice, and liver failure.
73	LUNGNOT09	Library was constructed using RNA isolated from the lung tissue of a 23-week-old Caucasian male fetus. The pregnancy was terminated following a diagnosis by ultrasound of infantile polycystic kidney disease.
74	PROSNOT15	Library was constructed using RNA isolated from diseased prostate tissue removed from a 66-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma (Gleason grade 2+3). The patient presented with elevated prostate specific antigen (PSA). Family history included prostate cancer, secondary bone cancer, and benign hypertension.
75	PROSNOT14	Library was constructed using RNA isolated from diseased prostate tissue removed from a 60-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma (Gleason grade 3+4). Family history included benign hypertension, cerebrovascular disease, and arteriosclerotic coronary artery disease.
76	SKINBIT01	Library was constructed using RNA isolated from diseased skin tissue of the left lower leg. Patient history included erythema nodosum of the left lower leg.
77	CORPNOT02	Library was constructed using RNA isolated from diseased corpus callosum tissue removed from the brain of a 74-year-old Caucasian male who died from Alzheimer's disease.
78	BRAITUT02	Library was constructed using RNA isolated from brain tumor tissue removed from the frontal lobe of a 58-year-old Caucasian male during excision of a cerebral meningeal lesion. Pathology indicated a grade 2 metastatic hypernephroma. Patient history included a grade 2 renal cell carcinoma, insomnia, and chronic airway obstruction. Family history included a malignant neoplasm of the kidney.

Table 4 (cont.)

79	BRSTNOT07	Library was constructed using RNA isolated from diseased breast tissue removed from a 43-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated mildly proliferative fibrocystic changes with epithelial hyperplasia, papillomatosis, and duct ectasia. Pathology for the associated tumor tissue indicated invasive grade 4, nuclear grade 3 mammary adenocarcinoma with extensive comedo necrosis. Family history included epilepsy, cardiovascular disease, and type II diabetes.
80	KIDNTUT13	Library was constructed using RNA isolated from kidney tumor tissue removed from a 51-year-old Caucasian female during a nephroureterectomy. Pathology indicated a grade 3 renal cell carcinoma. Family history included calculus of the kidney, colon cancer, and type II diabetes.
81	UTRSNOT16	Library was constructed using RNA isolated from uterine endometrial tissue removed from a 48-year-old Caucasian female during a vaginal hysterectomy, rectocele repair, and bilateral salpingo-oophorectomy. Pathology indicated chronic cervicitis, and the endometrium was weakly proliferative. Pathology for the associated tumor tissue indicated a single submucosal leiomyoma. Patient history included hyperlipidemia and meningitis. Family history included benign hypertension, hyperlipidemia, atrial fibrillation, atherosclerotic coronary artery disease, and type II diabetes.
82	UTRMTMT01	Library was constructed using RNA isolated from myometrial tissue removed from a 45-year-old Caucasian female during vaginal hysterectomy and bilateral salpingo-oophorectomy. Pathology indicated the myometrium was negative for tumor. Pathology for the associated tumor tissue indicated multiple (23) subserosal, intramural, and submucosal leiomyomata. Patient history included extrinsic asthma without status asthmaticus and normal delivery. Family history included cerebrovascular disease, depression, and atherosclerotic coronary artery disease.
83	EOSINOT03	This library was constructed using RNA isolated from pooled diseased eosinophils obtained from allergic asthmatic individuals.
84	EOSINOT02	This library was constructed using RNA isolated from pooled eosinophils obtained from allergic asthmatic individuals.
85	CRBLNOT01	This library was constructed using RNA isolated from the cerebellum tissue of a 69-year-old Caucasian male who died from chronic obstructive pulmonary disease. Patient history included myocardial infarction, hypertension, and osteoarthritis.
86	SYNOOAT01	This library was constructed using RNA isolated from the knee synovial membrane tissue of an 82-year-old female with osteoarthritis.
87	BRSTNOT03	This library was constructed using RNA isolated from diseased breast tissue removed from a 54-year-old Caucasian female during a bilateral radical mastectomy. Pathology for the associated tumor tissue indicated residual invasive grade 3 mammary ductal adenocarcinoma. Patient history included kidney infection and condyloma acuminatum.

		Family history included benign hypertension, hyperlipidemia, and a malignant neoplasm of the colon.
88	LUNGNOT03	This library was constructed using RNA isolated from lung tissue of a 79-year-old Caucasian male. Pathology for the associated tumor tissue indicated grade 4 carcinoma. Patient history included a benign prostate neoplasm and atherosclerosis.
89	COLNNOT13	This library was constructed using RNA isolated from ascending colon tissue of a 28-year-old Caucasian male with moderate chronic ulcerative colitis.
90	LATRTUT02	This library was constructed using RNA isolated from a myxoma removed from the left atrium of a 43-year-old Caucasian male during annuloplasty. Pathology indicated atrial myxoma. Patient history included pulmonary insufficiency, acute myocardial infarction, atherosclerotic coronary artery disease, hyperlipidemia, and tobacco use. Family history included benign hypertension, acute myocardial infarction, atherosclerotic coronary artery disease, and type II diabetes.
91	PROSNOT15	This library was constructed using RNA isolated from diseased prostate tissue removed from a 66-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma (Gleason grade 2+3). The patient presented with elevated prostate specific antigen (PSA). Family history included prostate cancer, secondary bone cancer, and benign hypertension.
92	PROSTUT10	This library was constructed using RNA isolated from prostatic tumor tissue removed from a 66-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated an adenocarcinoma (Gleason grade 2+3). Adenofibromatous hyperplasia was also present. The patient presented with elevated prostate specific antigen (PSA). Family history included prostate cancer and secondary bone cancer.
93	PROSTUT12	This library was constructed using RNA isolated from prostate tumor tissue removed from a 65-year-old Caucasian male during a radical prostatectomy. Pathology indicated an adenocarcinoma (Gleason grade 2+2). Adenofibromatous hyperplasia was also present. The patient presented with elevated prostate specific antigen (PSA).
94	TESTNOT03	This library was constructed using RNA isolated from testicular tissue removed from a 37-year-old Caucasian male, who died from liver disease. Patient history included cirrhosis, jaundice, and liver failure.
95	BRAINON01	This library was constructed and normalized from 4.88 million independent clones from a brain library. RNA was made from brain tissue removed from a 26-year-old Caucasian male during craniplasty and excision of a cerebral meningeal lesion. Pathology for the associated tumor tissue indicated a grade 4 oligoastrocytoma in the right fronto-parietal part of the brain.

Table 4 (cont.)

96	ISLTNOT01	This library was constructed using RNA isolated from a pooled collection of pancreatic islet cells.
97	COLWTUT16	This library was constructed using RNA isolated from colon tumor tissue obtained from a 60-year-old Caucasian male during a left hemicolectomy. Pathology indicated an invasive grade 2 adenocarcinoma, forming a sessile mass. Patient history included thrombophlebitis, inflammatory polyarthropathy, prostatic inflammatory disease, and depressive disorder. Previous surgeries included resection of the rectum. Family history included atherosclerotic coronary artery disease and colon cancer.
98	THYRNOT10	This library was constructed using RNA isolated from the diseased left thyroid tissue removed from a 30-year-old Caucasian female during a unilateral thyroid lobectomy and parathyroid reimplantation. Pathology indicated lymphocytic thyroiditis.
99	PROSBPT03	This library was constructed using RNA isolated from diseased prostate tissue removed from a 59-year-old Caucasian male during a radical prostatectomy and regional lymph node excision. Pathology indicated benign prostatic hyperplasia (BPH). Pathology for the associated tumor indicated adenocarcinoma, Gleason grade 3+3. The patient presented with elevated prostate specific antigen (PSA), benign hypertension, and hyperlipidemia. Family history included cerebrovascular disease, benign hypertension and prostate cancer.
100	BMARNOT03	This library was constructed using RNA isolated from the left tibial bone marrow tissue of a 16-year-old Caucasian male during a partial left tibial ostectomy with free skin graft. Patient history included an abnormality of the red blood cells. Family history included osteoarthritis.
101	UTRSNOT05	This library was constructed using RNA isolated from the uterine tissue of a 45-year-old Caucasian female during a total abdominal hysterectomy and total colectomy. Pathology for the associated tumor tissue indicated multiple leiomyomas of the myometrium and a grade 2 colonic adenocarcinoma of the cecum. Patient history included multiple sclerosis and mitral valve disorder. Family history included type I diabetes, cerebrovascular disease, atherosclerotic coronary artery disease, malignant skin neoplasm, hypertension, and malignant neoplasm of the colon.

Table 4 (cont.)

102	LUNGNOT35	This library was constructed using RNA isolated from lung tissue removed from a 62-year-old Caucasian female. Pathology for the associated tumor tissue indicated a grade 1 spindle cell carcinoid forming a nodule. Patient history included depression, thrombophlebitis, and hyperlipidemia. Family history included cerebrovascular disease, atherosclerotic coronary artery disease, breast cancer, colon cancer type II diabetes, and malignant skin melanoma.
103	THYMNOT11	This library was constructed using RNA isolated from thymus tissue removed from a 2-year-old Caucasian female during a thymectomy and patch closure of left atrioventricular fistula. The patient presented with congenital heart abnormalities. Patient history included double inlet left ventricle and a rudimentary right ventricle, pulmonary hypertension, cyanosis, subaortic stenosis, seizures, and a fracture of the skull base. Family history included reflux neuropathy.
104	KIDNNOT34	This library was constructed using RNA isolated from left kidney tissue obtained from an 8-year-old Caucasian male who died from an intracranial hemorrhage.

Table 5

Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25: 3389-3402.	*ESTs:* Probability value= 1.0E-8 or less *Full Length sequences*: Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises as least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad Sci. 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183: 63-98; and Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489.	*ESTs:* fasta E value=1.06E-6 *Assembled ESTs*: fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value=1.0E-8 or less *Full Length sequences:* fastx score=100 or greater
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S and J.G. Henikoff, Nucl. Acid Res., 19:6565-72, 1991. J.G. Henikoff and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37: 417-424.	Score=1000 or greater; Ratio of Score/Strength = 0.75 or larger; and, if applicable, Probability value= 1.0E-3 or less
HMMER	An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.	Score=10-50 bits for PFAM hits, depending on individual protein families

Table 5 (cont.)

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25: 217-221.	Normalized quality score≥GCG-specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1.
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M. S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater; Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12: 431-439.	Score=3.5 or greater
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch et al. supra; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

What is claimed is:

1. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

a) an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52,

b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52,

c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52, and

d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52.

2. An isolated polypeptide of claim 1 selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52.

3. An isolated polynucleotide encoding a polypeptide of claim 1.

4. An isolated polynucleotide encoding a polypeptide of claim 2.

5. An isolated polynucleotide of claim 4 selected from the group consisting of SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID

NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, and SEQ ID NO:104.

6. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.

7. A cell transformed with a recombinant polynucleotide of claim 6.

8. A transgenic organism comprising a recombinant polynucleotide of claim 6.

9. A method for producing a polypeptide of claim 1, the method comprising:

a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim 1, and

b) recovering the polypeptide so expressed.

10. An isolated antibody which specifically binds to a polypeptide of claim 1.

11. An isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of:

a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104,

b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104,

c) a polynucleotide sequence complementary to a),

d) a polynucleotide sequence complementary to b), and

e) an RNA equivalent of a)-d).

12. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 11.

13. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 11, the method comprising:

a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe

specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and

b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

14. A method of claim 13, wherein the probe comprises at least 60 contiguous nucleotides.

15. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 11, the method comprising:

a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and

b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

16. A pharmaceutical composition comprising an effective amount of a polypeptide of claim 1 and a pharmaceutically acceptable excipient.

17. A pharmaceutical composition of claim 16, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52.

18. A method for treating a disease or condition associated with decreased expression of functional INTRA, comprising administering to a patient in need of such treatment the pharmaceutical composition of claim 16.

19. A method for screening a compound for effectiveness as an agonist of a polypeptide of claim 1, the method comprising:

a) exposing a sample comprising a polypeptide of claim 1 to a compound, and

b) detecting agonist activity in the sample.

20. A pharmaceutical composition comprising an agonist compound identified by a method of claim 19 and a pharmaceutically acceptable excipient.

21. A method for treating a disease or condition associated with decreased expression of functional INTRA, comprising administering to a patient in need of such treatment a pharmaceutical composition of claim 20.

22. A method for screening a compound for effectiveness as an antagonist of a polypeptide of claim 1, the method comprising:

a) exposing a sample comprising a polypeptide of claim 1 to a compound, and

b) detecting antagonist activity in the sample.

23. A pharmaceutical composition comprising an antagonist compound identified by a method of claim 22 and a pharmaceutically acceptable excipient.

24. A method for treating a disease or condition associated with overexpression of functional INTRA, comprising administering to a patient in need of such treatment a pharmaceutical composition of claim 23.

25. A method of screening for a compound that specifically binds to the polypeptide of claim 1, said method comprising the steps of:

a) combining the polypeptide of claim 1 with at least one test compound under suitable conditions, and

b) detecting binding of the polypeptide of claim 1 to the test compound, thereby identifying a compound that specifically binds to the polypeptide of claim 1.

26. A method of screening for a compound that modulates the activity of the polypeptide of claim 1, said method comprising:

a) combining the polypeptide of claim 1 with at least one test compound under conditions permissive for the activity of the polypeptide of claim 1,

b) assessing the activity of the polypeptide of claim 1 in the presence of the test compound, and

c) comparing the activity of the polypeptide of claim 1 in the presence of the test compound with the activity of the polypeptide of claim 1 in the absence of the test compound, wherein a change in the activity of the polypeptide of claim 1 in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide of claim 1.

27 A method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 5, the method comprising:

a) exposing a sample comprising the target polynucleotide to a compound, and

b) detecting altered expression of the target polynucleotide.

28. A method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 5, the method comprising:

a) exposing a sample comprising the target polynucleotide to a compound, under conditions suitable for the expression of the target polynucleotide,

b) detecting altered expression of the target polynucleotide, and

c) comparing the expression of the target polynucleotide in the presence of varying amounts of the compound and in the absence of the compound.

29 A method for assessing toxicity of a test compound, said method comprising,

a) treating a biological sample containing nucleic acids with the test compound,

b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide of claim 11 under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence of a polynucleotide of claim 11 or fragment thereof,

c) quantifying the amount of hybridization complex; and

d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

30. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:1.

31. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:2.

32. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO 3

33. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO 4.

34. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO.5.

35 A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO.6.

36. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO 7

37. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:8.

38. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:9.

39. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:10.

40. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO.11.

41. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:12.

42. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO.13.

43 A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:14.

44 A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:15.

45. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO.16.

46. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:17.

47. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:18.

48. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:19.

49. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:20.

50. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO 21

51 A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO 22

52. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO.23

53. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO.24.

54. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO.25.

55. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:26

56. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO 27.

57. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO.28.

58. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:29.

59. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:30.

60 A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:31.

61. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:34.

62. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:35.

63. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO 36.

64. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO.37.

65. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO.38.

66. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:39.

67. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:40.

68. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:41

69. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:42

70. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:43.

71. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:44.

72. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO.45

73. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO 46.

74. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:47.

75. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:48

76 A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:49.

77. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:50.

78. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO:51.

79. A method of claim 9, wherein the polypeptide has the sequence of SEQ ID NO.52.

80. A diagnostic test for a condition or disease associated with the expression of human intracellular signaling molecules (INTRA) in a biological sample comprising the steps of:

a) combining the biological sample with an antibody of claim 10, under conditions suitable for the antibody to bind the polypeptide and form an antibody:polypeptide complex; and

b) detecting the complex, wherein the presence of the complex correlates with the presence of the polypeptide in the biological sample.

81 The antibody of claim 10, wherein the antibody is:

a) a chimeric antibody,

b) a single chain antibody,

c) a Fab fragment,

d) a $F(ab')_2$ fragment, or

e) a humanized antibody.

82. A composition comprising an antibody of claim 10 and an acceptable excipient

83. A method of diagnosing a condition or disease associated with the expression of human intracellular signaling molecules (INTRA) in a subject, comprising administering to said subject an effective amount of the composition of claim 82

84. A composition of claim 82, wherein the antibody is labeled.

85. A method of diagnosing a condition or disease associated with the expression of human intracellular signaling molecules (INTRA) in a subject, comprising administering to said subject an effective amount of the composition of claim 84.

86. A method of preparing a polyclonal antibody with the specificity of the antibody of claim 10 comprising:

a) immunizing an animal with a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO 3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO.8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO.12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO.22, SEQ ID NO 23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO.27, SEQ ID NO 28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO.31, SEQ ID NO:34, SEQ ID NO 35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO.38, SEQ ID NO.39, SEQ ID NO.40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO 44, SEQ ID NO 45, SEQ ID NO:46, SEQ ID NO.47, SEQ ID NO:48, SEQ ID NO 49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52,, or an immunogenic fragment thereof, under conditions to elicit an antibody response,

b) isolating antibodies from said animal, and

c) screening the isolated antibodies with the polypeptide, thereby identifying a polyclonal antibody which binds specifically to a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO.1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO.5, SEQ ID NO:6, SEQ ID NO.7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO.11, SEQ ID NO.12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO.16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO.21, SEQ ID NO.22, SEQ ID NO 23, SEQ ID

NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52.

87. An antibody produced by a method of claim 86.

88. A composition comprising the antibody of claim 87 and a suitable carrier

89. A method of making a monoclonal antibody with the specificity of the antibody of claim 10 comprising:

a) immunizing an animal with a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52., or an immunogenic fragment thereof, under conditions to elicit an antibody response;

b) isolating antibody producing cells from the animal;

c) fusing the antibody producing cells with immortalized cells to form monoclonal antibody-producing hybridoma cells;

d) culturing the hybridoma cells, and

e) isolating from the culture monoclonal antibody which binds specifically to a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID

NO:27, SEQ ID NO:28, SEQ ID NO 29, SEQ ID NO.30, SEQ ID NO 31, SEQ ID NO.34, SEQ ID NO.35, SEQ ID NO 36, SEQ ID NO.37, SEQ ID NO.38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO 41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO 48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52.

90. A monoclonal antibody produced by a method of claim 89.

91. A composition comprising the antibody of claim 90 and a suitable carrier

92. The antibody of claim 10, wherein the antibody is produced by screening a Fab expression library.

93 The antibody of claim 10, wherein the antibody is produced by screening a recombinant immunoglobulin library.

94. A method for detecting a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO.2, SEQ ID NO.3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO.20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO 24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO 27, SEQ ID NO.28, SEQ ID NO:29, SEQ ID NO.30, SEQ ID NO:31, SEQ ID NO.34, SEQ ID NO 35, SEQ ID NO.36, SEQ ID NO 37, SEQ ID NO.38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO 41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO 45, SEQ ID NO:46, SEQ ID NO 47, SEQ ID NO:48, SEQ ID NO.49, SEQ ID NO:50, SEQ ID NO.51, and SEQ ID NO.52 in a sample, comprising the steps of.

a) incubating the antibody of claim 10 with a sample under conditions to allow specific binding of the antibody and the polypeptide; and

b) detecting specific binding, wherein specific binding indicates the presence of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO.1, SEQ ID NO:2, SEQ ID NO.3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO 10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO.14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO.19, SEQ ID NO:20, SEQ ID NO.21, SEQ ID NO.22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO.26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID

NO:34. SEQ ID NO.35. SEQ ID NO.36. SEQ ID NO 37. SEQ ID NO 38. SEQ ID NO:39. SEQ ID NO 40. SEQ ID NO:41. SEQ ID NO 42. SEQ ID NO:43. SEQ IDNO 44. SEQ ID NO 45. SEQ ID NO:46. SEQ ID NO 47. SEQ ID NO:48. SEQ ID NO:49. SEQ ID NO 50. SEQ ID NO.51. and SEQ ID NO:52 in the sample

95 A method of purifying a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1. SEQ ID NO:2. SEQ ID NO.3. SEQ ID NO 4. SEQ ID NO:5. SEQ ID NO:6. SEQ ID NO:7. SEQ ID NO:8. SEQ ID NO.9. SEQ ID NO 10. SEQ ID NO:11. SEQ ID NO:12. SEQ ID NO:13. SEQ ID NO:14. SEQ ID NO.15. SEQ ID NO.16. SEQ ID NO 17. SEQ ID NO:18. SEQ ID NO:19. SEQ ID NO:20. SEQ ID NO:21. SEQ ID NO:22. SEQ ID NO 23. SEQ ID NO.24. SEQ ID NO:25. SEQ ID NO:26. SEQ ID NO:27. SEQ ID NO.28. SEQ ID NO 29. SEQ ID NO.30. SEQ ID NO:31. SEQ ID NO:34. SEQ ID NO.35. SEQ ID NO 36. SEQ ID NO 37. SEQ ID NO 38. SEQ ID NO:39. SEQ ID NO:40. SEQ ID NO 41. SEQ ID NO:42. SEQ ID NO 43. SEQ ID NO.44. SEQ ID NO:45. SEQ ID NO:46. SEQ ID NO.47. SEQ ID NO:48. SEQ ID NO:49. SEQ ID NO 50. SEQ ID NO:51. and SEQ ID NO:52 from a sample. the method comprising:

a) incubating the antibody of claim 10 with a sample under conditions to allow specific binding of the antibody and the polypeptide; and

b) separating the antibody from the sample and obtaining the purified polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1. SEQ ID NO.2. SEQ ID NO:3. SEQ ID NO:4. SEQ ID NO:5. SEQ ID NO.6. SEQ ID NO.7. SEQ ID NO:8. SEQ ID NO:9. SEQ ID NO:10. SEQ ID NO:11. SEQ ID NO.12. SEQ ID NO:13. SEQ ID NO:14. SEQ ID NO.15. SEQ ID NO 16. SEQ ID NO.17. SEQ ID NO.18. SEQ ID NO:19. SEQ ID NO.20. SEQ ID NO.21. SEQ ID NO.22. SEQ ID NO.23. SEQ ID NO:24. SEQ ID NO.25. SEQ ID NO.26. SEQ ID NO.27. SEQ ID NO:28. SEQ ID NO:29. SEQ ID NO.30. SEQ ID NO.31. SEQ ID NO:34. SEQ ID NO:35. SEQ ID NO:36. SEQ ID NO 37. SEQ ID NO:38. SEQ ID NO:39. SEQ ID NO:40. SEQ ID NO:41. SEQ ID NO 42. SEQ ID NO:43. SEQ ID NO 44. SEQ ID NO:45. SEQ ID NO 46. SEQ ID NO.47. SEQ ID NO 48. SEQ ID NO 49. SEQ ID NO:50. SEQ ID NO:51. and SEQ ID NO:52

96 A microarray wherein at least one element of the microarray is a polynucleotide of claim 12

97. A method for generating a transcript image of a sample which contains polynucleotides. the method comprising the steps of:

a) labeling the polynucleotides of the sample.

b) contacting the elements of the microarray of claim 96 with the labeled polynucleotides of the sample under conditions suitable for the formation of a hybridization complex, and

c) quantifying the expression of the polynucleotides in the sample.

98 An array comprising different nucleotide molecules affixed in distinct physical locations on a solid substrate, wherein at least one of said nucleotide molecules comprises a first oligonucleotide or polynucleotide sequence specifically hybridizable with at least 30 contiguous nucleotides of a target polynucleotide, said target polynucleotide having a sequence of claim 11

99. An array of claim 98, wherein said first oligonucleotide or polynucleotide sequence is completely complementary to at least 30 contiguous nucleotides of said target polynucleotide

100. An array of claim 98, wherein said first oligonucleotide or polynucleotide sequence is completely complementary to at least 60 contiguous nucleotides of said target polynucleotide

101. An array of claim 98, which is a microarray.

102. An array of claim 98, further comprising said target polynucleotide hybridized to said first oligonucleotide or polynucleotide.

103 An array of claim 98, wherein a linker joins at least one of said nucleotide molecules to said solid substrate.

104 An array of claim 98, wherein each distinct physical location on the substrate contains multiple nucleotide molecules having the same sequence, and each distinct physical location on the substrate contains nucleotide molecules having a sequence which differs from the sequence of nucleotide molecules at another physical location on the substrate.

105. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO.1.

106. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO.2.

107. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:3.

108 A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO.4.

109 A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:5

110. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO 6

111. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO 7

112. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO 8

113. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:9.

114. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO. 10.

115. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:11.

116. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO. 12.

117. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:13.

118. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:14.

119. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:15.

120. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:16.

121. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO. 17.

122. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:18.

123. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:19.

124 A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO 20.

125. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO.21.

126. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:22.

127. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:23.

128. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:24

129. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:25

130. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:26

131. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:27.

132. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:28

133. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:29.

134. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:30.

135. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:31.

136. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:34.

137. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:35.

138. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:36.

139. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:37.

140. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:38.

141. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:39.

142. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:40.

143. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:41.

144. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:42.

145. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:43.

146. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:44.

147. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO 45

148 A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO 46

149. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:47.

150. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO 48

151. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:49

152. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO.50.

153. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:51.

154. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:52.

155 A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:53.

156. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:54.

157. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO.55.

158. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO.56.

159 A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO.57

160 A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:58.

161. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:59.

162 A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:60

163 A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:61.

164. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO.62.

165. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:63

166. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO.64.

167. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO.65.

168. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO.66

169 A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO 67.

170. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO.68.

171 A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:69.

172. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:70.

173 A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO.71

174 A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO.72.

175. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:73

176 A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO.74.

177. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO 75

178 A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:76

179 A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO.77

180. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:78

181. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:79

182 A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:80.

183. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:81

184. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO.82.

185 A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO 83.

186. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:86.

187 A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:87.

188. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO.88.

189. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:89.

190. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:90.

191 A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:91.

192. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:92.

193. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:93

194 A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:94.

195. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:95.

196. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO 96.

197. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:97.

198. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:98

199. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO 99

200 A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:100.

201 A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:101.

202 A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:102

203. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:103.

204. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:104.

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(54) Title: INTRACELLULAR SIGNALING MOLECULES

(57) Abstract: The invention provides human intracellular signaling molecules (INTRA) and polynucleotides which identify and encode INTRA. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of INTRA.

PF-0733 USN

DECLARATION AND POWER OF ATTORNEY FOR UNITED STATES PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name, and

I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a United States patent is sought on the invention entitled

INTRACELLULAR SIGNALING MOLECULES

the specification of which:

/ X / is attached hereto.

/ __ / was filed on _____ as application Serial No. _____ and if this box contains an X / __ /, was amended on _____.

/ X / was filed as Patent Cooperation Treaty international application No. PCT/US00/16636 on June 16, 2000, if this box contains an X / _/, was amended on under Patent Cooperation Treaty Article 19 on _____ 2001, and if this box contains an X / _/, was amended on _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge my duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim the benefit under Title 35, United States Code, §119 or §365(a)-(b) of any foreign application(s) for patent or inventor's certificate indicated below and of any Patent Cooperation Treaty international applications(s) designating at least one country other than the United States indicated below and have also identified below any foreign application(s) for patent or inventor's certificate and Patent Cooperation Treaty international application(s) designating at least one country other than the United States for the same subject matter and having a filing date before that of the application for said subject matter the priority of which is claimed:

Country	Number	Filing Date	Priority Claimed
_____	_____	_____	/ / Yes / / No
_____	_____	_____	/ / Yes / / No

PF-0733 USN

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

Application Serial No.	Filed	Status (Pending, Abandoned, Patented)
60/139,566	June16, 1999	Expired
60/149,640	August 17, 1999	Expired
60/164,417	November 9, 1999	Expired

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in said prior application(s) in the manner required by the first paragraph of Title 35, United States Code §112, I acknowledge my duty to disclose material information as defined in Title 37 Code of Federal Regulations, §1.56(a) which occurred between the filing date(s) of the prior application(s) and the national or Patent Cooperation Treaty international filing date of this application:

Application Serial No.	Filed	Status (Pending, Abandoned, Patented)

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respectively and individually, as my patent attorneys and/or agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith. Please address all communications to:

PF-0733 USN

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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Arg Gln Ser Arg Met Pro Gln Glu Asp Glu Arg Pro Ala Asp Glu
            170                 175                 180
Tyr Asp Gln Pro Trp Glu Trp Lys Lys Asp His Ile Ser Arg Ala
```

```
                185                 190                 195
Phe Ala Val Gln Phe Asp Ser Pro Glu Trp Glu Arg Thr Pro Gly
                200                 205                 210
Ser Ala Lys Glu Leu Arg Arg Pro Pro Pro Arg Ser Pro Gln Pro
                215                 220                 225
Ala Glu Arg Val Asp Pro Ala Leu Pro Leu Glu Lys Gln Pro Trp
                230                 235                 240
Phe His Gly Pro Leu Asn Arg Ala Asp Ala Glu Ser Leu Leu Ser
                245                 250                 255
Leu Cys Lys Glu Gly Ser Tyr Leu Val Arg Leu Ser Glu Thr Ser
                260                 265                 270
Pro Gln Asp Cys Ser Leu Ser Leu Arg Ser Ser Gln Gly Phe Leu
                275                 280                 285
His Leu Lys Phe Ala Arg Thr Arg Glu Asn Gln Val Val Leu Gly
                290                 295                 300
Gln His Ser Gly Pro Phe Pro Ser Val Pro Glu Leu Val Leu His
                305                 310                 315
Tyr Ser Ser Arg Pro Leu Pro Val Gln Gly Ala Glu His Leu Ala
                320                 325                 330
Leu Leu Tyr Pro Val Val Thr Gln Thr Pro
                335                 340
<210> 3
<211> 353
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1418671CD1

<400> 3
Met Glu Asp Gly Val Leu Lys Glu Gly Phe Leu Val Lys Arg Gly
  1                 5                  10                  15
His Ile Val His Asn Trp Lys Ala Arg Trp Phe Ile Leu Arg Gln
                 20                  25                  30
Asn Thr Leu Val Tyr Tyr Lys Leu Glu Gly Gly Arg Arg Val Thr
                 35                  40                  45
Pro Pro Lys Gly Arg Ile Leu Leu Asp Gly Cys Thr Ile Thr Cys
                 50                  55                  60
Pro Cys Leu Glu Tyr Glu Asn Arg Pro Leu Leu Ile Lys Leu Lys
                 65                  70                  75
Thr Gln Thr Ser Thr Glu Tyr Phe Leu Glu Ala Cys Ser Arg Glu
                 80                  85                  90
Glu Arg Asp Ala Trp Ala Phe Glu Ile Thr Gly Ala Ile His Ala
                 95                 100                 105
Gly Gln Pro Gly Lys Val Gln Gln Leu His Ser Leu Arg Asn Ser
                110                 115                 120
Phe Lys Leu Pro Pro His Ile Ser Leu His Arg Ile Val Asp Lys
                125                 130                 135
Met His Asp Ser Asn Thr Gly Ile Arg Ser Ser Pro Asn Met Glu
                140                 145                 150
Gln Gly Ser Thr Tyr Lys Lys Thr Phe Leu Gly Ser Ser Leu Val
                155                 160                 165
Asp Trp Leu Ile Ser Asn Ser Phe Thr Ala Ser Arg Leu Glu Ala
                170                 175                 180
Val Thr Leu Ala Ser Met Leu Met Glu Glu Asn Phe Leu Arg Pro
                185                 190                 195
Val Gly Val Arg Ser Met Gly Ala Ile Arg Ser Gly Asp Leu Ala
                200                 205                 210
Glu Gln Phe Leu Asp Asp Ser Thr Ala Leu Tyr Thr Phe Ala Glu
                215                 220                 225
Ser Tyr Lys Lys Lys Ile Ser Pro Lys Glu Glu Ile Ser Leu Ser
                230                 235                 240
Thr Val Glu Leu Ser Gly Thr Val Val Lys Gln Gly Tyr Leu Ala
                245                 250                 255
Lys Gln Gly His Lys Arg Lys Asn Trp Lys Val Arg Arg Phe Val
                260                 265                 270
```

```
Leu Arg Lys Asp Pro Ala Phe Leu His Tyr Tyr Asp Pro Ser Lys
                275                 280                 285
Glu Glu Asn Arg Pro Val Gly Gly Phe Ser Leu Arg Gly Ser Leu
            290                 295                 300
Val Ser Ala Leu Glu Asp Asn Gly Val Pro Thr Gly Val Lys Gly
        305                 310                 315
Asn Val Gln Gly Asn Leu Phe Lys Val Ile Thr Lys Asp Asp Thr
                320                 325                 330
His Tyr Tyr Ile Gln Ala Ser Ser Lys Ala Glu Arg Ala Glu Trp
            335                 340                 345
Ile Glu Ala Ile Lys Lys Leu Thr
        350
```

<210> 4
<211> 593
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1456841CD1

<400> 4

```
Met Ser Arg Pro Ser Ser Arg Ala Ile Tyr Leu His Arg Lys Glu
  1               5                  10                  15
Tyr Ser Gln Asn Leu Thr Ser Glu Pro Thr Leu Leu Gln His Arg
            20                  25                  30
Val Glu His Leu Met Thr Cys Lys Gln Gly Ser Gln Arg Val Gln
        35                  40                  45
Gly Pro Glu Asp Ala Leu Gln Lys Leu Phe Glu Met Asp Ala Gln
    50                  55                  60
Gly Arg Val Trp Ser Gln Asp Leu Ile Leu Gln Val Arg Asp Gly
65                  70                  75
Trp Leu Gln Leu Leu Asp Ile Glu Thr Lys Glu Glu Leu Asp Ser
                80                  85                  90
Tyr Arg Leu Asp Ser Ile Gln Ala Met Asn Val Ala Leu Asn Thr
            95                 100                 105
Cys Ser Tyr Asn Ser Ile Leu Ser Ile Thr Val Gln Glu Pro Gly
        110                 115                 120
Leu Pro Gly Thr Ser Thr Leu Leu Phe Gln Cys Gln Glu Val Gly
    125                 130                 135
Ala Glu Arg Leu Lys Thr Ser Leu Gln Lys Ala Leu Glu Glu Glu
140                 145                 150
Leu Glu Gln Arg Pro Arg Leu Gly Gly Leu Gln Pro Ser Gln Asp
155                 160                 165
Arg Trp Arg Gly Pro Ala Met Glu Arg Pro Leu Pro Met Glu Gln
                170                 175                 180
Ala Arg Tyr Leu Glu Pro Gly Ile Pro Pro Glu Gln Pro His Gln
            185                 190                 195
Arg Thr Leu Glu His Ser Leu Pro Pro Ser Pro Arg Pro Leu Pro
        200                 205                 210
Arg His Thr Ser Ala Arg Glu Pro Ser Ala Phe Thr Leu Pro Pro
    215                 220                 225
Pro Arg Arg Ser Ser Ser Pro Glu Asp Pro Glu Arg Asp Glu Glu
230                 235                 240
Val Leu Asn His Val Leu Arg Asp Ile Glu Leu Phe Met Gly Lys
245                 250                 255
Leu Glu Lys Ala Gln Ala Lys Thr Ser Arg Lys Lys Lys Phe Gly
            260                 265                 270
Lys Lys Asn Lys Asp Gln Gly Gly Leu Thr Gln Ala Gln Tyr Ile
        275                 280                 285
Asp Cys Phe Gln Lys Ile Lys Tyr Ser Phe Asn Leu Leu Gly Arg
    290                 295                 300
Leu Ala Thr Trp Leu Lys Glu Thr Ser Ala Pro Glu Leu Val His
305                 310                 315
Ile Leu Phe Lys Ser Leu Asn Phe Ile Leu Ala Arg Cys Pro Glu
                320                 325                 330
Ala Gly Leu Ala Ala Gln Val Ile Ser Pro Leu Leu Thr Pro Lys
```

```
                335                 340                 345
Ala Ile Asn Leu Leu Gln Ser Cys Leu Ser Pro Pro Glu Ser Asn
                350                 355                 360
Leu Trp Met Gly Leu Gly Pro Ala Trp Thr Thr Ser Arg Ala Asp
                365                 370                 375
Trp Thr Gly Asp Glu Pro Leu Pro Tyr Gln Pro Thr Phe Ser Asp
                380                 385                 390
Asp Trp Gln Leu Pro Glu Pro Ser Ser Gln Ala Pro Leu Gly Tyr
                395                 400                 405
Gln Asp Pro Val Ser Leu Arg Arg Gly Ser His Arg Leu Gly Ser
                410                 415                 420
Thr Ser His Phe Pro Gln Glu Lys Thr His Asn His Asp Pro Gln
                425                 430                 435
Pro Gly Asp Pro Asn Ser Arg Pro Ser Ser Pro Lys Pro Ala Gln
                440                 445                 450
Pro Ala Leu Lys Met Gln Val Leu Tyr Glu Phe Glu Ala Arg Asn
                455                 460                 465
Pro Arg Glu Leu Thr Val Val Gln Gly Glu Lys Leu Glu Val Leu
                470                 475                 480
Asp His Ser Lys Arg Trp Trp Leu Val Lys Asn Glu Ala Gly Arg
                485                 490                 495
Ser Gly Tyr Ile Pro Ser Asn Ile Leu Glu Pro Leu Gln Pro Gly
                500                 505                 510
Thr Pro Gly Thr Gln Gly Gln Ser Pro Ser Arg Val Pro Met Leu
                515                 520                 525
Arg Leu Ser Ser Arg Pro Glu Glu Val Thr Asp Trp Leu Gln Ala
                530                 535                 540
Glu Asn Phe Ser Thr Ala Thr Val Arg Thr Leu Gly Ser Leu Thr
                545                 550                 555
Gly Ser Gln Leu Leu Arg Ile Arg Pro Gly Glu Leu Gln Met Leu
                560                 565                 570
Cys Pro Gln Glu Ala Pro Arg Ile Leu Ser Arg Leu Glu Ala Val
                575                 580                 585
Arg Arg Met Leu Gly Ile Ser Pro
                590
```

<210> 5
<211> 358
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2020010CD1

<400> 5

```
Met Ala Gly Pro Gly Pro Thr Phe Pro Leu His Arg Leu Val Trp
  1                 5                  10                  15
Ala Asn Arg His Arg Glu Leu Glu Ala Ala Leu His Ser His Gln
                 20                  25                  30
His Asp Ile Glu Gln Glu Asp Pro Arg Gly Arg Thr Pro Leu Glu
                 35                  40                  45
Leu Ala Val Ser Leu Gly Asn Leu Glu Ser Val Arg Val Leu Leu
                 50                  55                  60
Arg His Asn Ala Asn Val Gly Lys Glu Asn Arg Gln Gly Trp Ala
                 65                  70                  75
Val Leu Gln Glu Ala Val Ser Thr Gly Asp Pro Glu Met Val Gln
                 80                  85                  90
Leu Val Leu Gln Tyr Arg Asp Tyr Gln Arg Ala Thr Gln Arg Leu
                 95                 100                 105
Ala Gly Ile Pro Glu Leu Leu Asn Lys Leu Arg Gln Ala Pro Asp
                110                 115                 120
Phe Tyr Val Glu Met Lys Trp Glu Phe Thr Ser Trp Val Pro Leu
                125                 130                 135
Val Ser Lys Met Cys Pro Ser Asp Val Tyr Arg Val Trp Lys Arg
                140                 145                 150
Gly Glu Ser Leu Arg Val Asp Thr Ser Leu Leu Gly Phe Glu His
                155                 160                 165
```

Met Thr Trp Gln Arg Gly Arg Arg Ser Phe Ile Phe Lys Gly Gln
170 175 180
Glu Ala Gly Ala Leu Val Met Glu Val Asp His Asp Arg Gln Val
185 190 195
Val His Val Glu Thr Leu Gly Leu Thr Leu Gln Glu Pro Glu Thr
200 205 210
Leu Leu Ala Ala Met Arg Pro Ser Glu Glu His Val Ala Ser Arg
215 220 225
Leu Thr Ser Pro Ile Val Ser Thr His Leu Asp Thr Arg Asn Val
230 235 240
Ala Phe Glu Arg Asn Lys Cys Gly Ile Trp Gly Trp Arg Ser Glu
245 250 255
Lys Met Glu Thr Val Ser Gly Tyr Glu Ala Lys Val Tyr Ser Ala
260 265 270
Thr Asn Val Glu Leu Val Thr Arg Thr Arg Thr Glu His Leu Ser
275 280 285
Asp Gln Asp Lys Ser Arg Ser Lys Ala Gly Lys Thr Pro Phe Gln
290 295 300
Ser Phe Leu Gly Met Ala Gln Gln His Ser Ser His Thr Gly Ala
305 310 315
Pro Val Gln Gln Ala Ala Ser Pro Thr Asn Pro Thr Ala Ile Ser
320 325 330
Pro Glu Glu Tyr Phe Asp Pro Asn Phe Ser Leu Glu Ser Arg Asn
335 340 345
Ile Gly Arg Pro Ile Glu Met Ser Ser Lys Val Gln Arg
350 355

<210> 6
<211> 749
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2149037CD1

<400> 6
Met Ser Gly Ser His Thr Pro Ala Cys Gly Pro Phe Ser Ala Leu
1 5 10 15
Thr Pro Ser Ile Trp Pro Gln Glu Ile Leu Ala Lys Tyr Thr Gln
20 25 30
Lys Glu Glu Ser Ala Glu Gln Pro Glu Phe Tyr Tyr Asp Glu Phe
35 40 45
Gly Phe Arg Val Tyr Lys Glu Glu Gly Asp Glu Pro Gly Ser Ser
50 55 60
Leu Leu Ala Asn Ser Pro Leu Met Glu Asp Ala Pro Gln Arg Leu
65 70 75
Arg Trp Gln Ala His Leu Glu Phe Thr His Asn His Asp Val Gly
80 85 90
Asp Leu Thr Trp Asp Lys Ile Ala Val Ser Leu Pro Arg Ser Glu
95 100 105
Lys Leu Arg Ser Leu Val Leu Ala Gly Ile Pro His Gly Met Arg
110 115 120
Pro Gln Leu Trp Met Arg Leu Ser Gly Ala Leu Gln Lys Lys Arg
125 130 135
Asn Ser Glu Leu Ser Tyr Arg Glu Ile Val Lys Asn Ser Ser Asn
140 145 150
Asp Glu Thr Ile Ala Ala Lys Gln Ile Glu Lys Asp Leu Leu Arg
155 160 165
Thr Met Pro Ser Asn Ala Cys Phe Ala Ser Met Gly Ser Ile Gly
170 175 180
Val Pro Arg Leu Arg Arg Val Leu Arg Ala Leu Ala Trp Leu Tyr
185 190 195
Pro Glu Ile Gly Tyr Cys Gln Gly Thr Gly Met Val Ala Ala Cys
200 205 210
Leu Leu Leu Phe Leu Glu Glu Glu Asp Ala Phe Trp Met Met Ser
215 220 225
Ala Ile Ile Glu Asp Leu Leu Pro Ala Ser Tyr Phe Ser Thr Thr

```
                    230                 235                 240
Leu Leu Gly Val Gln Thr Asp Gln Arg Val Leu Arg His Leu Ile
                    245                 250                 255
Val Gln Tyr Leu Pro Arg Leu Asp Lys Leu Leu Gln Glu His Asp
                    260                 265                 270
Ile Glu Leu Ser Leu Ile Thr Leu His Trp Phe Leu Thr Ala Phe
                    275                 280                 285
Ala Ser Val Val Asp Ile Lys Leu Leu Leu Arg Ile Trp Asp Leu
                    290                 295                 300
Phe Phe Tyr Glu Gly Ser Arg Val Leu Phe Gln Leu Thr Leu Gly
                    305                 310                 315
Met Leu His Leu Lys Glu Glu Glu Leu Ile Gln Ser Glu Asn Ser
                    320                 325                 330
Ala Ser Ile Phe Asn Thr Leu Ser Asp Ile Pro Ser Gln Met Glu
                    335                 340                 345
Asp Ala Glu Leu Leu Leu Gly Val Ala Met Arg Leu Ala Gly Ser
                    350                 355                 360
Leu Thr Asp Val Ala Val Glu Thr Gln Arg Arg Lys His Leu Ala
                    365                 370                 375
Tyr Leu Ile Ala Asp Gln Gly Gln Leu Leu Gly Ala Gly Thr Leu
                    380                 385                 390
Thr Asn Leu Ser Gln Val Val Arg Arg Arg Thr Gln Arg Arg Lys
                    395                 400                 405
Ser Thr Ile Thr Ala Leu Leu Phe Gly Glu Asp Asp Leu Glu Ala
                    410                 415                 420
Leu Lys Ala Lys Asn Ile Lys Gln Thr Glu Leu Val Ala Asp Leu
                    425                 430                 435
Arg Glu Ala Ile Leu Arg Val Ala Arg His Phe Gln Cys Thr Asp
                    440                 445                 450
Pro Lys Asn Cys Ser Val Glu Leu Thr Pro Asp Tyr Ser Met Glu
                    455                 460                 465
Ser His Gln Arg Asp His Glu Asn Tyr Val Ala Cys Ser Arg Ser
                    470                 475                 480
His Arg Arg Arg Ala Lys Ala Leu Leu Asp Phe Glu Arg His Asp
                    485                 490                 495
Asp Asp Glu Leu Gly Phe Arg Lys Asn Asp Ile Ile Thr Ile Val
                    500                 505                 510
Ser Gln Lys Asp Glu His Cys Trp Val Gly Glu Leu Asn Gly Leu
                    515                 520                 525
Arg Gly Trp Phe Pro Ala Lys Phe Val Glu Val Leu Asp Glu Arg
                    530                 535                 540
Ser Lys Glu Tyr Ser Ile Ala Gly Asp Asp Ser Val Thr Glu Gly
                    545                 550                 555
Val Thr Asp Leu Val Arg Gly Thr Leu Cys Pro Ala Leu Lys Ala
                    560                 565                 570
Leu Phe Glu His Gly Leu Lys Lys Pro Ser Leu Leu Gly Gly Ala
                    575                 580                 585
Cys His Pro Trp Leu Phe Ile Glu Glu Ala Ala Gly Arg Glu Val
                    590                 595                 600
Glu Arg Asp Phe Ala Ser Val Tyr Ser Arg Leu Val Leu Cys Lys
                    605                 610                 615
Thr Phe Arg Leu Asp Glu Asp Gly Lys Val Leu Thr Pro Glu Glu
                    620                 625                 630
Leu Leu Tyr Arg Ala Val Gln Ser Val Asn Val Thr His Asp Ala
                    635                 640                 645
Val His Ala Gln Met Asp Val Lys Leu Arg Ser Leu Ile Cys Val
                    650                 655                 660
Gly Leu Asn Glu Gln Val Leu His Leu Trp Leu Glu Val Leu Cys
                    665                 670                 675
Ser Ser Leu Pro Thr Val Glu Lys Trp Tyr Gln Pro Trp Ser Phe
                    680                 685                 690
Leu Arg Ser Pro Gly Trp Val Gln Ile Lys Cys Glu Leu Arg Val
                    695                 700                 705
Leu Cys Cys Phe Ala Phe Ser Leu Ser Gln Asp Trp Glu Leu Pro
                    710                 715                 720
Ala Lys Arg Glu Ala Gln Gln Pro Leu Lys Glu Gly Val Arg Asp
                    725                 730                 735
```

Met Leu Val Lys His His Leu Phe Ser Trp Asp Val Asp Gly
740 745

<210> 7
<211> 139
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2162179CD1

<400> 7
Met Ala Asp Glu Lys Asp Arg Glu Glu Ile Ile Val Ala Glu Phe
1 5 10 15
His Lys Lys Ile Lys Glu Ala Phe Glu Val Phe Asp His Glu Ser
20 25 30
Asn Asn Thr Val Asp Val Arg Glu Ile Gly Thr Ile Ile Arg Ser
35 40 45
Leu Gly Cys Cys Pro Thr Glu Gly Glu Leu His Asp Leu Ile Ala
50 55 60
Glu Val Glu Glu Glu Glu Pro Thr Gly Tyr Ile Arg Phe Glu Lys
65 70 75
Phe Leu Pro Val Met Thr Glu Ile Leu Leu Glu Arg Lys Tyr Arg
80 85 90
Pro Ile Pro Glu Asp Val Leu Leu Arg Ala Phe Glu Val Leu Asp
95 100 105
Ser Ala Lys Arg Gly Phe Leu Thr Lys Asp Glu Leu Ile Lys Tyr
110 115 120
Met Thr Glu Glu Gly Lys Cys Asp Leu Leu Leu Ile Thr Met Thr
125 130 135
Tyr Val Arg Asn

<210> 8
<211> 539
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2244706CD1

<400> 8
Met Val Gly Lys Pro Val His Lys Gly Ser Glu Ser Pro Asn Ser
1 5 10 15
Phe Leu Asp Gln Glu Tyr Arg Lys Arg Phe Asn Ile Val Glu Glu
20 25 30
Asp Thr Val Leu Tyr Cys Tyr Glu Tyr Glu Lys Gly Arg Ser Ser
35 40 45
Ser Gln Gly Arg Arg Glu Ser Thr Pro Thr Tyr Gly Lys Leu Arg
50 55 60
Pro Ile Ser Met Pro Val Glu Tyr Asn Trp Val Gly Asp Tyr Glu
65 70 75
Asp Pro Asn Lys Met Lys Arg Asp Ser Arg Arg Glu Asn Ser Leu
80 85 90
Leu Arg Tyr Met Ser Asn Glu Lys Ile Ala Gln Glu Glu Tyr Met
95 100 105
Phe Gln Arg Asn Ser Lys Lys Asp Thr Gly Lys Lys Ser Lys Lys
110 115 120
Lys Gly Asp Lys Ser Asn Ser Pro Thr His Tyr Ser Leu Leu Pro
125 130 135
Ser Leu Gln Met Asp Ala Leu Arg Gln Asp Ile Met Gly Thr Pro
140 145 150
Val Pro Glu Thr Thr Leu Tyr His Thr Phe Gln Gln Ser Ser Leu
155 160 165
Gln His Lys Ser Lys Lys Lys Asn Lys Gly Pro Ile Ala Gly Lys
170 175 180
Ser Lys Arg Arg Ile Ser Cys Lys Asp Leu Gly Arg Gly Asp Cys

```
                185                 190                 195
Glu Gly Trp Leu Trp Lys Lys Lys Asp Ala Lys Ser Tyr Phe Ser
                200                 205                 210
Gln Lys Trp Lys Lys Tyr Trp Phe Val Leu Lys Asp Ala Ser Leu
                215                 220                 225
Tyr Trp Tyr Ile Asn Glu Glu Asp Glu Lys Ala Glu Gly Phe Ile
                230                 235                 240
Ser Leu Pro Glu Phe Lys Ile Asp Arg Ala Ser Glu Cys Arg Lys
                245                 250                 255
Lys Tyr Ala Phe Lys Ala Cys His Pro Lys Ile Lys Ser Phe Tyr
                260                 265                 270
Phe Ala Ala Glu His Leu Asp Asp Met Asn Arg Trp Leu Asn Arg
                275                 280                 285
Ile Asn Met Leu Thr Ala Gly Tyr Ala Glu Arg Glu Arg Ile Lys
                290                 295                 300
Gln Glu Gln Asp Tyr Trp Ser Glu Ser Asp Lys Glu Glu Ala Asp
                305                 310                 315
Thr Pro Ser Thr Pro Lys Gln Asp Ser Pro Pro Pro Pro Tyr Asp
                320                 325                 330
Thr Tyr Pro Arg Pro Pro Ser Met Ser Cys Ala Ser Pro Tyr Val
                335                 340                 345
Glu Ala Lys His Ser Arg Leu Ser Ser Thr Glu Thr Ser Gln Ser
                350                 355                 360
Gln Ser Ser His Glu Glu Phe Arg Gln Glu Val Thr Gly Ser Ser
                365                 370                 375
Ala Val Ser Pro Ile Arg Lys Thr Ala Ser Gln Arg Arg Ser Trp
                380                 385                 390
Gln Asp Leu Ile Glu Thr Pro Leu Thr Ser Ser Gly Leu His Tyr
                395                 400                 405
Leu Gln Thr Leu Pro Leu Glu Asp Ser Val Phe Ser Asp Ser Ala
                410                 415                 420
Ala Ile Ser Pro Glu His Arg Arg Gln Ser Thr Leu Pro Thr Gln
                425                 430                 435
Lys Cys His Leu Gln Asp His Tyr Gly Pro Tyr Pro Leu Ala Glu
                440                 445                 450
Ser Glu Met Met Gln Val Leu Asn Gly Asn Gly Gly Lys Pro Arg
                455                 460                 465
Arg Phe Thr Leu Pro Arg Asp Ser Gly Phe Asn His Cys Cys Leu
                470                 475                 480
Asn Ala Pro Val Ser Ala Cys Asp Pro Gln Asp Asp Val Gln Pro
                485                 490                 495
Pro Glu Val Glu Glu Glu Glu Asp Asp Glu Glu Glu Ala Trp Glu
                500                 505                 510
Ala Ala Gly Gly Asn Met Gly Glu Lys Ser Leu Phe Thr Ala Arg
                515                 520                 525
Val Gly Arg Pro Phe Met Gln Asn Gly Ser Thr Leu Trp His
                530                 535
```

<210> 9
<211> 319
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2316805CD1

```
<400> 9
Met Asp Pro Gln Asn Gln His Gly Ser Gly Ser Ser Leu Val Val
  1               5                  10                  15
Ile Gln Gln Pro Ser Leu Asp Ser Arg Gln Arg Leu Asp Tyr Glu
             20                  25                  30
Arg Glu Ile Gln Pro Thr Ala Ile Leu Ser Leu Asp Gln Ile Lys
             35                  40                  45
Ala Ile Arg Gly Ser Asn Glu Tyr Thr Glu Gly Pro Ser Val Val
             50                  55                  60
Lys Arg Pro Ala Pro Arg Thr Ala Pro Arg Gln Glu Lys His Glu
             65                  70                  75
```

```
Arg Thr His Glu Ile Ile Pro Ile Asn Val Asn Asn Asn Tyr Glu
                80                  85                  90
His Arg His Thr Ser His Leu Gly His Ala Val Leu Pro Ser Asn
                95                 100                 105
Ala Arg Gly Pro Ile Leu Ser Arg Ser Thr Ser Thr Gly Ser Ala
               110                 115                 120
Ala Ser Ser Gly Ser Asn Ser Ser Ala Ser Ser Glu Gln Gly Leu
               125                 130                 135
Leu Gly Arg Ser Pro Pro Thr Arg Pro Val Pro Gly His Arg Ser
               140                 145                 150
Glu Arg Ala Ile Arg Thr Gln Pro Lys Gln Leu Ile Val Asp Asp
               155                 160                 165
Leu Lys Gly Ser Leu Lys Glu Asp Leu Thr Gln His Lys Phe Ile
               170                 175                 180
Cys Glu Gln Cys Gly Lys Cys Lys Cys Gly Glu Cys Thr Ala Pro
               185                 190                 195
Arg Thr Leu Pro Ser Cys Leu Ala Cys Asn Arg Gln Cys Leu Cys
               200                 205                 210
Ser Ala Glu Ser Met Val Glu Tyr Gly Thr Cys Met Cys Leu Val
               215                 220                 225
Lys Gly Ile Phe Tyr His Cys Ser Asn Asp Asp Glu Gly Asp Ser
               230                 235                 240
Tyr Ser Asp Asn Pro Cys Ser Cys Ser Gln Ser His Cys Cys Ser
               245                 250                 255
Arg Tyr Leu Cys Met Gly Ala Met Ser Leu Phe Leu Pro Cys Leu
               260                 265                 270
Leu Cys Tyr Pro Pro Ala Lys Gly Cys Leu Lys Leu Cys Arg Arg
               275                 280                 285
Cys Tyr Asp Trp Ile His Arg Pro Gly Cys Arg Cys Lys Asn Ser
               290                 295                 300
Asn Thr Val Tyr Cys Lys Leu Glu Ser Cys Pro Ser Arg Gly Gln
               305                 310                 315
Gly Lys Pro Ser
```

<210> 10
<211> 747
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2320010CD1

```
<400> 10
Met Gly Lys Arg Asn Ile Ala Arg Val His Asp Ala Trp Leu Ser
  1               5                  10                  15
Lys His Phe Gly Ile Asp Arg Lys Ser Gln Thr Met Pro Ala Leu
                20                  25                  30
Arg Asn Arg Ser Gly Val Met Gln Ala Arg Leu Gln His Leu Ser
                35                  40                  45
Ser Leu Glu Ser Ser Phe Thr Leu Asn His Ser Ser Thr Thr Thr
                50                  55                  60
Glu Ala Asp Ile Phe His Gln Ala Leu Leu Ala Ala Asn Thr Ala
                65                  70                  75
Thr Glu Val Ser Leu Thr Val Leu Asp Thr Ile Ser Phe Phe Thr
                80                  85                  90
Gln Cys Phe Lys Thr Gln Leu Leu Asn Asn Asp Gly His Asn Pro
                95                 100                 105
Leu Met Lys Lys Val Phe Asp Ile His Leu Ala Phe Leu Lys Asn
               110                 115                 120
Gly Gln Ser Glu Val Ser Leu Lys His Val Phe Ala Ser Leu Arg
               125                 130                 135
Ala Phe Ile Ser Lys Phe Pro Ser Ala Phe Phe Lys Gly Arg Val
               140                 145                 150
Asn Met Cys Ala Ala Phe Cys Tyr Glu Val Leu Lys Cys Cys Thr
               155                 160                 165
Ser Lys Ile Ser Ser Thr Arg Asn Glu Ala Ser Ala Leu Leu Tyr
```

```
                170                 175                 180
Leu Leu Met Arg Asn Asn Phe Glu Tyr Thr Lys Arg Lys Thr Phe
                185                 190                 195
Leu Arg Thr His Leu Gln Ile Ile Ile Ala Val Ser Gln Leu Ile
                200                 205                 210
Ala Asp Val Ala Leu Ser Gly Gly Ser Arg Phe Gln Glu Ser Leu
                215                 220                 225
Phe Ile Ile Asn Asn Phe Ala Asn Ser Asp Arg Pro Met Lys Ala
                230                 235                 240
Thr Ala Phe Pro Ala Glu Val Lys Asp Leu Thr Lys Arg Ile Arg
                245                 250                 255
Thr Val Leu Met Ala Thr Ala Gln Met Lys Glu His Glu Lys Asp
                260                 265                 270
Pro Glu Met Leu Ile Asp Leu Gln Tyr Ser Leu Ala Lys Ser Tyr
                275                 280                 285
Ala Ser Thr Pro Glu Leu Arg Lys Thr Trp Leu Asp Ser Met Ala
                290                 295                 300
Lys Ile His Val Lys Asn Gly Asp Phe Ser Glu Ala Ala Met Cys
                305                 310                 315
Tyr Val His Val Ala Ala Leu Val Ala Glu Phe Leu His Arg Lys
                320                 325                 330
Lys Leu Phe Pro Asn Gly Cys Ser Ala Phe Lys Lys Ile Thr Pro
                335                 340                 345
Asn Ile Asp Glu Glu Gly Ala Met Lys Glu Asp Ala Gly Met Met
                350                 355                 360
Asp Val His Tyr Ser Glu Glu Val Leu Leu Glu Leu Leu Glu Gln
                365                 370                 375
Cys Val Asp Gly Leu Trp Lys Ala Glu Arg Tyr Glu Ile Ile Ser
                380                 385                 390
Glu Ile Ser Lys Leu Ile Val Pro Ile Tyr Glu Lys Arg Arg Glu
                395                 400                 405
Phe Glu Lys Leu Thr Gln Val Tyr Arg Thr Leu His Gly Ala Tyr
                410                 415                 420
Thr Lys Ile Leu Glu Val Met His Thr Lys Lys Arg Leu Leu Gly
                425                 430                 435
Thr Phe Phe Arg Val Ala Phe Tyr Gly Gln Ser Phe Phe Glu Glu
                440                 445                 450
Glu Asp Gly Lys Glu Tyr Ile Tyr Lys Glu Pro Lys Leu Thr Gly
                455                 460                 465
Leu Ser Glu Ile Ser Leu Arg Leu Val Lys Leu Tyr Gly Glu Lys
                470                 475                 480
Phe Gly Thr Glu Asn Val Lys Ile Ile Gln Asp Ser Asp Lys Val
                485                 490                 495
Asn Ala Lys Glu Leu Asp Pro Lys Tyr Ala His Ile Gln Val Thr
                500                 505                 510
Tyr Val Lys Pro Tyr Phe Asp Asp Lys Glu Leu Thr Glu Arg Lys
                515                 520                 525
Thr Glu Phe Glu Arg Asn His Asn Ile Ser Arg Phe Val Phe Glu
                530                 535                 540
Ala Pro Tyr Thr Leu Ser Gly Lys Lys Gln Gly Cys Ile Glu Glu
                545                 550                 555
Gln Cys Lys Arg Arg Thr Ile Leu Thr Thr Ser Asn Ser Phe Pro
                560                 565                 570
Tyr Val Lys Lys Arg Ile Pro Ile Asn Cys Glu Gln Gln Ile Asn
                575                 580                 585
Leu Lys Pro Ile Asp Val Ala Thr Asp Glu Ile Lys Asp Lys Thr
                590                 595                 600
Ala Glu Leu Gln Lys Leu Cys Ser Ser Thr Asp Val Asp Met Ile
                605                 610                 615
Gln Leu Gln Leu Lys Leu Gln Gly Cys Val Ser Val Gln Val Asn
                620                 625                 630
Ala Gly Pro Leu Ala Tyr Ala Arg Ala Phe Leu Asn Asp Ser Gln
                635                 640                 645
Ala Ser Lys Tyr Pro Pro Lys Lys Val Ser Glu Leu Lys Asp Met
                650                 655                 660
Phe Arg Lys Phe Ile Gln Ala Cys Ser Ile Ala Leu Glu Leu Asn
                665                 670                 675
```

Glu Arg Leu Ile Lys Glu Asp Gln Val Glu Tyr His Glu Gly Leu
680 685 690
Lys Ser Asn Phe Arg Asp Met Val Lys Glu Leu Ser Asp Ile Ile
695 700 705
His Glu Gln Ile Leu Gln Glu Asp Thr Met His Ser Pro Trp Met
710 715 720
Ser Asn Thr Leu His Val Phe Cys Ala Ile Ser Gly Thr Ser Ser
725 730 735
Asp Arg Gly Tyr Gly Ser Pro Arg Tyr Ala Glu Val
740 745

<210> 11
<211> 266
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2564901CD1

<400> 11
Met Gln Gly Ser Thr Arg Arg Met Gly Val Met Thr Asp Val His
1 5 10 15
Arg Arg Phe Leu Gln Leu Leu Met Thr His Gly Val Leu Glu Glu
20 25 30
Trp Asp Val Lys Arg Leu Gln Thr His Cys Tyr Lys Val His Asp
35 40 45
Arg Asn Ala Thr Val Asp Lys Leu Glu Asp Phe Ile Asn Asn Ile
50 55 60
Asn Ser Val Leu Glu Ser Leu Tyr Ile Glu Ile Lys Arg Gly Val
65 70 75
Thr Glu Asp Asp Gly Arg Pro Ile Tyr Ala Leu Val Asn Leu Ala
80 85 90
Thr Thr Ser Ile Ser Lys Met Ala Thr Asp Phe Ala Glu Asn Glu
95 100 105
Leu Asp Leu Phe Arg Lys Ala Leu Glu Leu Ile Ile Asp Ser Glu
110 115 120
Thr Gly Phe Ala Ser Ser Thr Asn Ile Leu Asn Leu Val Asp Gln
125 130 135
Leu Lys Gly Lys Lys Met Arg Lys Lys Glu Ala Glu Gln Val Leu
140 145 150
Gln Lys Phe Val Gln Asn Lys Trp Leu Ile Glu Lys Glu Gly Glu
155 160 165
Phe Thr Leu His Gly Arg Ala Ile Leu Glu Met Glu Gln Tyr Ile
170 175 180
Arg Glu Thr Tyr Pro Asp Ala Val Lys Ile Cys Asn Ile Cys His
185 190 195
Ser Leu Leu Ile Gln Gly Gln Ser Cys Glu Thr Cys Gly Ile Arg
200 205 210
Met His Leu Pro Cys Val Ala Lys Tyr Phe Gln Ser Asn Ala Glu
215 220 225
Pro Arg Cys Pro His Cys Asn Asp Tyr Trp Pro His Glu Ile Pro
230 235 240
Lys Val Phe Asp Pro Glu Lys Glu Arg Glu Ser Gly Val Leu Lys
245 250 255
Ser Asn Lys Lys Ser Leu Arg Ser Arg Gln His
260 265

<210> 12
<211> 345
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2615168CD1

<400> 12
Met Ser Val Thr Gly Gly Lys Met Ala Pro Ser Leu Thr Gln Glu

```
  1               5                  10                  15
Ile Leu Ser His Leu Gly Leu Ala Ser Lys Thr Ala Ala Trp Gly
             20                  25                  30
Thr Leu Gly Thr Leu Arg Thr Phe Leu Asn Phe Ser Val Asp Lys
         35                  40                  45
Asp Ala Gln Arg Leu Leu Arg Ala Ile Thr Gly Gln Gly Val Asp
     50                  55                  60
Arg Ser Ala Ile Val Asp Val Leu Thr Asn Arg Ser Arg Glu Gln
 65                  70                  75
Arg Gln Leu Ile Ser Arg Asn Phe Gln Glu Arg Thr Gln Gln Asp
             80                  85                  90
Leu Met Lys Ser Leu Gln Ala Ala Leu Ser Gly Asn Leu Glu Arg
         95                 100                 105
Ile Val Met Ala Leu Leu Gln Pro Thr Ala Gln Phe Asp Ala Gln
        110                 115                 120
Glu Leu Arg Thr Ala Leu Lys Ala Ser Asp Ser Ala Val Asp Val
    125                 130                 135
Ala Ile Glu Ile Leu Ala Thr Arg Thr Pro Pro Gln Leu Gln Glu
    140                 145                 150
Cys Leu Ala Val Tyr Lys His Asn Phe Gln Val Glu Ala Val Asp
155                 160                 165
Asp Ile Thr Ser Glu Thr Ser Gly Ile Leu Gln Asp Leu Leu Leu
            170                 175                 180
Ala Leu Ala Lys Gly Gly Arg Asp Ser Tyr Ser Gly Ile Ile Asp
        185                 190                 195
Tyr Asn Leu Ala Glu Gln Asp Val Gln Ala Leu Gln Arg Ala Glu
    200                 205                 210
Gly Pro Ser Arg Glu Glu Thr Trp Val Pro Val Phe Thr Gln Arg
215                 220                 225
Asn Pro Glu His Leu Ile Arg Val Phe Asp Gln Tyr Gln Arg Ser
            230                 235                 240
Thr Gly Gln Glu Leu Glu Glu Ala Val Gln Asn Arg Phe His Gly
        245                 250                 255
Asp Ala Gln Val Ala Leu Leu Gly Leu Ala Ser Val Ile Lys Asn
    260                 265                 270
Thr Pro Leu Tyr Phe Ala Asp Lys Leu His Gln Ala Leu Gln Glu
275                 280                 285
Thr Glu Pro Asn Tyr Gln Val Leu Ile Arg Ile Leu Ile Ser Arg
            290                 295                 300
Cys Glu Thr Asp Leu Leu Ser Ile Arg Ala Glu Phe Arg Lys Lys
        305                 310                 315
Phe Gly Lys Ser Leu Tyr Ser Ser Leu Gln Asp Ala Val Lys Gly
    320                 325                 330
Asp Cys Gln Ser Ala Leu Leu Ala Leu Cys Arg Ala Glu Asp Met
335                 340                 345
```

<210> 13
<211> 437
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2658329CD1

<400> 13

```
Met Glu Lys Glu Leu Arg Ser Thr Ile Leu Phe Asn Ala Tyr Lys
  1               5                  10                  15
Lys Glu Ile Phe Thr Thr Asn Asn Gly Tyr Lys Ser Met Gln Lys
             20                  25                  30
Lys Leu Arg Ser Asn Trp Lys Ile Gln Ser Leu Lys Asp Glu Ile
         35                  40                  45
Thr Ser Glu Lys Leu Asn Gly Val Lys Leu Trp Ile Thr Ala Gly
     50                  55                  60
Pro Arg Glu Lys Phe Thr Ala Ala Glu Phe Glu Ile Leu Lys Lys
 65                  70                  75
Tyr Leu Asp Thr Gly Gly Asp Val Phe Val Met Leu Gly Glu Gly
```

```
                 80                  85                  90
Gly Glu Ser Arg Phe Asp Thr Asn Ile Asn Phe Leu Leu Glu Glu
                 95                 100                 105
Tyr Gly Ile Met Val Asn Asn Asp Ala Val Val Arg Asn Val Tyr
                110                 115                 120
His Lys Tyr Phe His Pro Lys Glu Ala Leu Val Ser Ser Gly Val
                125                 130                 135
Leu Asn Arg Glu Ile Ser Arg Ala Ala Gly Lys Ala Val Pro Gly
                140                 145                 150
Ile Ile Asp Glu Glu Ser Ser Gly Asn Asn Ala Gln Ala Leu Thr
                155                 160                 165
Phe Val Tyr Pro Phe Gly Ala Thr Leu Ser Val Met Lys Pro Ala
                170                 175                 180
Val Ala Val Leu Ser Thr Gly Ser Val Cys Phe Pro Leu Asn Arg
                185                 190                 195
Pro Ile Leu Ala Phe Tyr His Ser Lys Asn Gln Gly Gly Lys Leu
                200                 205                 210
Ala Val Leu Gly Ser Cys His Met Phe Ser Asp Gln Tyr Leu Asp
                215                 220                 225
Lys Glu Glu Asn Ser Lys Ile Met Asp Val Val Phe Gln Trp Leu
                230                 235                 240
Thr Thr Gly Asp Ile His Leu Asn Gln Ile Asp Ala Glu Asp Pro
                245                 250                 255
Glu Ile Ser Asp Tyr Met Met Leu Pro Tyr Thr Ala Thr Leu Ser
                260                 265                 270
Lys Arg Asn Arg Glu Cys Leu Gln Glu Ser Asp Glu Ile Pro Arg
                275                 280                 285
Asp Phe Thr Thr Leu Phe Asp Leu Ser Ile Phe Gln Leu Asp Thr
                290                 295                 300
Thr Ser Phe His Ser Val Ile Glu Ala His Glu Gln Leu Asn Val
                305                 310                 315
Lys His Glu Pro Leu Gln Leu Ile Gln Pro Gln Phe Glu Thr Pro
                320                 325                 330
Leu Pro Thr Leu Gln Pro Ala Val Phe Pro Pro Ser Phe Arg Glu
                335                 340                 345
Leu Pro Pro Pro Pro Leu Glu Leu Phe Asp Leu Asp Glu Thr Phe
                350                 355                 360
Ser Ser Glu Lys Ala Arg Leu Ala Gln Ile Thr Asn Lys Cys Thr
                365                 370                 375
Glu Glu Asp Leu Glu Phe Tyr Val Arg Lys Cys Gly Asp Ile Leu
                380                 385                 390
Gly Val Thr Ser Lys Leu Pro Lys Asp Gln Gln Asp Ala Lys His
                395                 400                 405
Ile Leu Glu His Val Phe Phe Gln Val Val Glu Phe Lys Lys Leu
                410                 415                 420
Asn Gln Glu His Asp Ile Asp Thr Ser Glu Thr Ala Phe Gln Asn
                425                 430                 435
Asn Phe
```

<210> 14
<211> 441
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2708944CD1

<400> 14

```
Met Val His Ile Lys Lys Gly Glu Leu Thr Gln Glu Glu Lys Glu
  1                 5                  10                  15
Leu Leu Glu Val Ile Gly Lys Gly Thr Val Gln Glu Ala Gly Thr
                 20                  25                  30
Leu Leu Ser Ser Lys Asn Val Arg Val Asn Cys Leu Asp Glu Asn
                 35                  40                  45
Gly Met Thr Pro Leu Met His Ala Ala Tyr Lys Gly Lys Leu Asp
                 50                  55                  60
```

```
Met Cys Lys Leu Leu Leu Arg His Gly Ala Asp Val Asn Cys His
                65                  70                  75
Gln His Glu His Gly Tyr Thr Ala Leu Met Phe Ala Ala Leu Ser
                80                  85                  90
Gly Asn Lys Asp Ile Thr Trp Val Met Leu Glu Ala Gly Ala Glu
                95                 100                 105
Thr Asp Val Val Asn Ser Val Gly Arg Thr Ala Ala Gln Met Ala
               110                 115                 120
Ala Phe Val Gly Gln His Asp Cys Val Thr Ile Ile Asn Asn Phe
               125                 130                 135
Phe Pro Arg Glu Arg Leu Asp Tyr Tyr Thr Lys Pro Gln Gly Leu
               140                 145                 150
Asp Lys Glu Pro Lys Leu Pro Pro Lys Leu Ala Gly Pro Leu His
               155                 160                 165
Lys Ile Ile Thr Thr Thr Asn Leu His Pro Val Lys Ile Val Met
               170                 175                 180
Leu Val Asn Glu Asn Pro Leu Leu Thr Glu Glu Ala Ala Leu Asn
               185                 190                 195
Lys Cys Tyr Arg Val Met Asp Leu Ile Cys Glu Lys Cys Met Lys
               200                 205                 210
Gln Arg Asp Met Asn Glu Val Leu Ala Met Lys Met His Tyr Ile
               215                 220                 225
Ser Cys Ile Phe Gln Lys Cys Ile Asn Phe Leu Lys Asp Gly Glu
               230                 235                 240
Asn Lys Leu Asp Thr Leu Ile Lys Ser Leu Leu Lys Gly Arg Ala
               245                 250                 255
Ser Asp Gly Phe Pro Val Tyr Gln Glu Lys Ile Ile Arg Glu Ser
               260                 265                 270
Ile Arg Lys Phe Pro Tyr Cys Glu Ala Thr Leu Leu Gln Gln Leu
               275                 280                 285
Val Arg Ser Ile Ala Pro Val Glu Ile Gly Ser Asp Pro Thr Ala
               290                 295                 300
Phe Ser Val Leu Thr Gln Ala Ile Thr Gly Gln Val Gly Phe Val
               305                 310                 315
Asp Val Glu Phe Cys Thr Thr Cys Gly Glu Lys Gly Ala Ser Lys
               320                 325                 330
Arg Cys Ser Val Cys Lys Met Val Ile Tyr Cys Asp Gln Thr Cys
               335                 340                 345
Gln Lys Thr His Trp Phe Thr His Lys Lys Ile Cys Lys Asn Leu
               350                 355                 360
Lys Asp Ile Tyr Glu Lys Gln Gln Leu Glu Ala Ala Lys Glu Lys
               365                 370                 375
Arg Gln Glu Glu Asn His Gly Lys Leu Asp Val Asn Ser Asn Cys
               380                 385                 390
Val Asn Glu Glu Gln Pro Glu Ala Glu Val Gly Ile Ser Gln Lys
               395                 400                 405
Asp Ser Asn Pro Glu Asp Ser Gly Glu Gly Lys Lys Glu Ser Leu
               410                 415                 420
Glu Ser Glu Ala Glu Leu Glu Gly Leu Gln Asp Ala Pro Ala Gly
               425                 430                 435
Pro Gln Val Ser Glu Glu
               440
```

<210> 15
<211> 487
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3315012CD1

<400> 15

```
Met Leu Arg Ala Pro Gly Cys Leu Leu Arg Thr Ser Val Ala Pro
  1               5                  10                  15
Ala Ala Ala Leu Ala Ala Ala Leu Leu Ser Ser Leu Ala Arg Cys
             20                  25                  30
Ser Leu Leu Glu Pro Arg Asp Pro Val Ala Ser Ser Leu Ser Pro
```

```
                35                  40                  45
Tyr Phe Gly Thr Lys Thr Arg Tyr Glu Asp Val Asn Pro Val Leu
                50                  55                  60
Leu Ser Gly Pro Glu Ala Pro Trp Arg Asp Pro Glu Leu Leu Glu
                65                  70                  75
Gly Thr Cys Thr Pro Val Gln Leu Val Ala Leu Ile Arg His Gly
                80                  85                  90
Thr Arg Tyr Pro Thr Val Lys Gln Ile Arg Lys Leu Arg Gln Leu
                95                 100                 105
His Gly Leu Leu Gln Ala Arg Gly Ser Arg Asp Gly Gly Ala Ser
               110                 115                 120
Ser Thr Gly Ser Arg Asp Leu Gly Ala Ala Leu Ala Asp Trp Pro
               125                 130                 135
Leu Trp Tyr Ala Asp Trp Met Asp Gly Gln Leu Val Glu Lys Gly
               140                 145                 150
Arg Gln Asp Met Arg Gln Leu Ala Leu Arg Leu Ala Ser Leu Phe
               155                 160                 165
Pro Val Leu Phe Ser Arg Glu Asn Tyr Gly Arg Leu Arg Leu Ile
               170                 175                 180
Thr Ser Ser Lys His Arg Cys Met Asp Ser Ser Ala Ala Phe Leu
               185                 190                 195
Gln Gly Leu Trp Gln His Tyr His Pro Gly Leu Pro Pro Pro Asp
               200                 205                 210
Val Ala Asp Met Glu Phe Gly Pro Pro Thr Val Asn Asp Lys Leu
               215                 220                 225
Met Arg Phe Phe Asp His Cys Glu Lys Phe Leu Thr Glu Val Glu
               230                 235                 240
Lys Asn Ala Thr Ala Leu Tyr His Val Glu Ala Phe Lys Thr Gly
               245                 250                 255
Pro Glu Met Gln Asn Ile Leu Lys Lys Val Ala Ala Thr Leu Gln
               260                 265                 270
Val Pro Val Asn Asp Leu Asn Ala Asp Leu Ile Gln Val Ala Phe
               275                 280                 285
Phe Thr Cys Ser Phe Asp Leu Ala Ile Lys Gly Val Lys Ser Pro
               290                 295                 300
Trp Cys Asp Val Phe Asp Ile Asp Asp Ala Lys Val Leu Glu Tyr
               305                 310                 315
Leu Asn Asp Leu Lys Gln Tyr Trp Lys Arg Gly Tyr Gly Tyr Thr
               320                 325                 330
Ile Asn Ser Arg Ser Ser Cys Thr Leu Phe Gln Asp Ile Phe Gln
               335                 340                 345
His Leu Asp Lys Ala Val Glu Gln Lys Gln Arg Ser Gln Pro Ile
               350                 355                 360
Ser Ser Pro Val Ile Leu Gln Phe Gly His Ala Glu Thr Leu Leu
               365                 370                 375
Pro Leu Leu Ser Leu Met Gly Tyr Phe Lys Asp Lys Glu Pro Leu
               380                 385                 390
Thr Ala Tyr Asn Tyr Lys Lys Gln Met His Arg Lys Phe Arg Ser
               395                 400                 405
Gly Leu Ile Val Pro Tyr Ala Ser Asn Leu Ile Phe Val Leu Tyr
               410                 415                 420
His Cys Glu Asn Ala Lys Thr Pro Lys Glu Gln Phe Arg Val Gln
               425                 430                 435
Met Leu Leu Asn Glu Lys Val Leu Pro Leu Ala Tyr Ser Gln Glu
               440                 445                 450
Thr Val Ser Phe Tyr Glu Asp Leu Lys Asn His Tyr Lys Asp Ile
               455                 460                 465
Leu Gln Ser Cys Gln Thr Ser Glu Glu Cys Glu Leu Ala Arg Ala
               470                 475                 480
Asn Ser Thr Ser Asp Glu Leu
               485
```

<210> 16
<211> 282
<212> PRT
<213> Homo sapiens

<220>

<221> misc_feature
<223> Incyte ID No: 4155412CD1

<400> 16
Met Val Leu Gly Lys Val Lys Ser Leu Thr Ile Ser Phe Asp Cys
1 5 10 15
Leu Asn Asp Ser Asn Val Pro Val Tyr Ser Ser Gly Asp Thr Val
20 25 30
Ser Gly Arg Val Asn Leu Glu Val Thr Gly Glu Ile Arg Val Lys
35 40 45
Ser Leu Lys Ile His Ala Arg Gly His Ala Lys Val Arg Trp Thr
50 55 60
Glu Ser Arg Asn Ala Gly Ser Asn Thr Ala Tyr Thr Gln Asn Tyr
65 70 75
Thr Glu Glu Val Glu Tyr Phe Asn His Lys Asp Ile Leu Ile Gly
80 85 90
His Glu Arg Asp Asp Asp Asn Ser Glu Glu Gly Phe His Thr Ile
95 100 105
His Ser Gly Arg His Glu Tyr Ala Phe Ser Phe Glu Leu Pro Gln
110 115 120
Thr Pro Leu Ala Thr Ser Phe Glu Gly Arg His Gly Ser Val Arg
125 130 135
Tyr Trp Val Lys Ala Glu Leu His Arg Pro Trp Leu Leu Pro Val
140 145 150
Lys Leu Lys Lys Glu Phe Thr Val Phe Glu His Ile Asp Ile Asn
155 160 165
Thr Pro Ser Leu Leu Ser Pro Gln Ala Gly Thr Lys Glu Lys Thr
170 175 180
Leu Cys Cys Trp Phe Cys Thr Ser Gly Pro Ile Ser Leu Ser Ala
185 190 195
Lys Ile Glu Arg Lys Gly Tyr Thr Pro Gly Glu Ser Ile Gln Ile
200 205 210
Phe Ala Glu Ile Glu Asn Cys Ser Ser Arg Met Val Val Pro Arg
215 220 225
Gln Pro Phe Thr Lys His Arg Pro Ser Ile Ala Lys Gly Lys Leu
230 235 240
Arg Glu Leu Asn Ser Leu Trp Leu Thr Cys Val Gly Asn Ser Leu
245 250 255
Thr Ser Gly Lys Asn Arg Asp Val Glu Met Ala Ser Leu Leu Lys
260 265 270
Ile Ser Asn Ser Phe Pro Pro Ser Asn Ala Ser Asn
275 280

<210> 17
<211> 581
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 4831840CD1

<400> 17
Met Ala Val Ala Gly Ala Val Ser Gly Glu Pro Leu Val His Trp
1 5 10 15
Cys Thr Gln Gln Leu Arg Lys Thr Phe Gly Leu Asp Val Ser Glu
20 25 30
Glu Ile Ile Gln Tyr Val Leu Ser Ile Glu Ser Ala Glu Glu Ile
35 40 45
Arg Glu Tyr Val Thr Asp Leu Leu Gln Gly Asn Glu Gly Lys Lys
50 55 60
Gly Gln Phe Ile Glu Glu Leu Ile Thr Lys Trp Gln Lys Asn Asp
65 70 75
Gln Glu Leu Ile Ser Asp Pro Leu Gln Gln Cys Phe Lys Lys Asp
80 85 90
Glu Ile Leu Asp Gly Gln Lys Ser Gly Asp His Leu Lys Arg Gly
95 100 105
Arg Lys Lys Gly Arg Asn Arg Gln Glu Val Pro Ala Phe Thr Glu

```
                    110                 115                 120
Pro Asp Thr Thr Ala Glu Val Lys Thr Pro Phe Asp Leu Ala Lys
                125                 130                 135
Ala Gln Glu Asn Ser Asn Ser Val Lys Lys Lys Thr Lys Phe Val
                140                 145                 150
Asn Leu Tyr Thr Arg Glu Gly Gln Asp Arg Leu Ala Val Leu Leu
                155                 160                 165
Pro Gly Arg His Pro Cys Asp Cys Leu Gly Gln Lys His Lys Leu
                170                 175                 180
Ile Asn Asn Cys Leu Ile Cys Gly Arg Ile Val Cys Glu Gln Glu
                185                 190                 195
Gly Ser Gly Pro Cys Leu Phe Cys Gly Thr Leu Val Cys Thr His
                200                 205                 210
Glu Glu Gln Asp Ile Leu Gln Arg Asp Ser Asn Lys Ser Gln Lys
                215                 220                 225
Leu Leu Lys Lys Leu Met Ser Gly Val Glu Asn Ser Gly Lys Val
                230                 235                 240
Asp Ile Ser Thr Lys Asp Leu Leu Pro His Gln Glu Leu Arg Ile
                245                 250                 255
Lys Ser Gly Leu Glu Lys Ala Ile Lys His Lys Asp Lys Leu Leu
                260                 265                 270
Glu Phe Asp Arg Thr Ser Ile Arg Arg Thr Gln Val Ile Asp Asp
                275                 280                 285
Glu Ser Asp Tyr Phe Ala Ser Asp Ser Asn Gln Trp Leu Ser Lys
                290                 295                 300
Leu Glu Arg Glu Thr Leu Gln Lys Arg Glu Glu Glu Leu Arg Glu
                305                 310                 315
Leu Arg His Ala Ser Arg Leu Ser Lys Lys Val Thr Ile Asp Phe
                320                 325                 330
Ala Gly Arg Lys Ile Leu Glu Glu Glu Asn Ser Leu Ala Glu Tyr
                335                 340                 345
His Ser Arg Leu Asp Glu Thr Ile Gln Ala Ile Ala Asn Gly Thr
                350                 355                 360
Leu Asn Gln Pro Leu Thr Lys Leu Asp Arg Ser Ser Glu Glu Pro
                365                 370                 375
Leu Gly Val Leu Val Asn Pro Asn Met Tyr Gln Ser Pro Pro Gln
                380                 385                 390
Trp Val Asp His Thr Gly Ala Ala Ser Gln Lys Lys Ala Phe Arg
                395                 400                 405
Ser Ser Gly Phe Gly Leu Glu Phe Asn Ser Phe Gln His Gln Leu
                410                 415                 420
Arg Ile Gln Asp Gln Glu Phe Gln Glu Gly Phe Asp Gly Gly Trp
                425                 430                 435
Cys Leu Ser Val His Gln Pro Trp Ala Ser Leu Leu Val Arg Gly
                440                 445                 450
Ile Lys Arg Val Glu Gly Arg Ser Trp Tyr Thr Pro His Arg Gly
                455                 460                 465
Arg Leu Trp Ile Ala Ala Thr Ala Lys Lys Pro Ser Pro Gln Glu
                470                 475                 480
Val Ser Glu Leu Gln Ala Thr Tyr Arg Leu Leu Arg Gly Lys Asp
                485                 490                 495
Val Glu Phe Pro Asn Asp Tyr Pro Ser Gly Cys Leu Leu Gly Cys
                500                 505                 510
Val Asp Leu Ile Asp Cys Leu Ser Gln Lys Gln Phe Lys Glu Gln
                515                 520                 525
Phe Pro Asp Ile Ser Gln Glu Ser Asp Ser Pro Phe Val Phe Ile
                530                 535                 540
Cys Lys Asn Pro Gln Glu Met Val Val Lys Phe Pro Ile Lys Gly
                545                 550                 555
Asn Pro Lys Ile Trp Lys Leu Asp Ser Lys Ile His Gln Gly Ala
                560                 565                 570
Lys Lys Gly Leu Met Lys Gln Asn Lys Ala Val
                575                 580
```

<210> 18
<211> 530
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 5676581CD1

<400> 18

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Met Thr Thr Arg Pro Thr Ala Val Lys Ala Thr Gly Gly Leu Cys
  1               5                  10                  15
Leu Leu Gly Ala Tyr Ala Asp Ser Asp Asp Asp Asn Asp Val
             20                  25                  30
Ser Glu Lys Leu Ala Gln Ser Lys Glu Thr Asn Gly Asn Gln Ser
         35                  40                  45
Thr Asp Ile Asp Ser Thr Leu Ala Asn Phe Leu Ala Glu Ile Asp
     50                  55                  60
Ala Ile Thr Ala Pro Gln Pro Ala Ala Pro Val Gly Ala Ser Ala
 65                  70                  75
Pro Pro Pro Thr Pro Pro Arg Pro Glu Pro Lys Glu Ala Ala Thr
             80                  85                  90
Ser Thr Leu Ser Ser Ser Thr Ser Asn Gly Thr Asp Ser Thr Gln
         95                 100                 105
Thr Ser Gly Trp Gln Tyr Asp Thr Gln Cys Ser Leu Ala Gly Val
    110                 115                 120
Gly Ile Glu Met Gly Asp Trp Gln Glu Val Trp Asp Glu Asn Thr
    125                 130                 135
Gly Cys Tyr Tyr Tyr Trp Asn Thr Gln Thr Asn Glu Val Thr Trp
    140                 145                 150
Glu Leu Pro Gln Tyr Leu Ala Thr Gln Val Gln Gly Leu Gln His
    155                 160                 165
Tyr Gln Pro Ser Ser Val Pro Gly Ala Glu Thr Ser Phe Val Val
    170                 175                 180
Asn Thr Asp Ile Tyr Ser Lys Glu Lys Thr Ile Ser Val Ser Ser
    185                 190                 195
Ser Lys Ser Gly Pro Val Ile Ala Lys Arg Glu Val Lys Lys Glu
    200                 205                 210
Val Asn Glu Gly Ile Gln Ala Leu Ser Asn Ser Glu Glu Glu Lys
    215                 220                 225
Lys Gly Val Ala Ala Ser Leu Leu Ala Pro Leu Leu Pro Glu Gly
    230                 235                 240
Ile Lys Glu Glu Glu Glu Arg Trp Arg Arg Lys Val Ile Cys Lys
    245                 250                 255
Glu Glu Pro Val Ser Glu Val Lys Glu Thr Ser Thr Thr Val Glu
    260                 265                 270
Glu Ala Thr Thr Ile Val Lys Pro Gln Glu Ile Met Leu Asp Asn
    275                 280                 285
Ile Glu Asp Pro Ser Gln Glu Asp Leu Cys Ser Val Val Gln Ser
    290                 295                 300
Gly Glu Ser Glu Glu Glu Glu Glu Gln Asp Thr Leu Glu Leu Glu
    305                 310                 315
Leu Val Leu Glu Arg Lys Lys Ala Glu Leu Arg Ala Leu Glu Glu
    320                 325                 330
Gly Asp Gly Ser Val Ser Gly Ser Ser Pro Arg Ser Asp Ile Ser
    335                 340                 345
Gln Pro Ala Ser Gln Asp Gly Met Arg Arg Leu Met Ser Lys Arg
    350                 355                 360
Gly Lys Trp Lys Met Phe Val Arg Ala Thr Ser Pro Glu Ser Thr
    365                 370                 375
Ser Arg Ser Ser Ser Lys Thr Gly Arg Asp Thr Pro Glu Asn Gly
    380                 385                 390
Glu Thr Ala Ile Gly Ala Glu Asn Ser Glu Lys Ile Asp Glu Asn
    395                 400                 405
Ser Asp Lys Glu Met Glu Val Glu Glu Ser Pro Glu Lys Ile Lys
    410                 415                 420
Val Gln Thr Thr Pro Lys Val Glu Glu Glu Gln Asp Leu Lys Phe
    425                 430                 435
Gln Ile Gly Glu Leu Ala Asn Thr Leu Thr Ser Lys Phe Glu Phe
    440                 445                 450
Leu Gly Ile Asn Arg Gln Ser Ile Ser Asn Phe His Val Leu Leu
    455                 460                 465
```

Leu Gln Thr Glu Thr Arg Ile Ala Asp Trp Arg Glu Gly Ala Leu
470 475 480
Asn Gly Asn Tyr Leu Lys Arg Lys Leu Gln Asp Ala Ala Glu Gln
485 490 495
Leu Lys Gln Tyr Glu Ile Asn Ala Thr Pro Lys Gly Trp Ser Cys
500 505 510
His Trp Asp Arg Tyr Ala Leu Phe Ser Pro Phe His Leu Ser Pro
515 520 525
Leu Thr Ser Gln Thr
530

<210> 19
<211> 475
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 034159CD1

<400> 19
Met Gln Lys Ser Thr Asn Ser Asp Thr Ser Val Glu Thr Leu Asn
1 5 10 15
Ser Thr Arg Gln Gly Thr Gly Ala Val Gln Met Arg Ile Lys Asn
20 25 30
Ala Asn Ser His His Asp Arg Leu Ser Gln Ser Lys Ser Met Ile
35 40 45
Leu Thr Asp Val Gly Lys Val Thr Glu Pro Ile Ser Arg His Arg
50 55 60
Arg Asn His Ser Gln His Ile Leu Lys Asp Val Ile Pro Pro Leu
65 70 75
Glu Gln Leu Met Val Glu Lys Glu Gly Tyr Leu Gln Lys Ala Lys
80 85 90
Ile Ala Asp Gly Gly Lys Lys Leu Arg Lys Asn Trp Ser Thr Ser
95 100 105
Trp Ile Val Leu Ser Ser Arg Arg Ile Glu Phe Tyr Lys Glu Ser
110 115 120
Lys Gln Gln Ala Leu Ser Asn Met Lys Thr Gly His Lys Pro Glu
125 130 135
Ser Val Asp Leu Cys Gly Ala His Ile Glu Trp Ala Lys Glu Lys
140 145 150
Ser Ser Arg Lys Asn Val Phe Gln Ile Thr Thr Val Ser Gly Asn
155 160 165
Glu Phe Leu Leu Gln Ser Asp Ile Asp Phe Ile Ile Leu Asp Trp
170 175 180
Phe His Ala Ile Lys Asn Ala Ile Asp Arg Leu Pro Lys Asp Ser
185 190 195
Ser Cys Pro Ser Arg Asn Leu Glu Leu Phe Lys Ile Gln Arg Ser
200 205 210
Ser Ser Thr Glu Leu Leu Ser His Tyr Asp Ser Asp Ile Lys Glu
215 220 225
Gln Lys Pro Glu His Arg Lys Ser Leu Met Phe Arg Leu His His
230 235 240
Ser Ala Ser Asp Thr Ser Asp Lys Asn Arg Val Lys Ser Arg Leu
245 250 255
Lys Lys Phe Ile Thr Arg Arg Pro Ser Leu Lys Thr Leu Gln Glu
260 265 270
Lys Gly Leu Ile Lys Asp Gln Ile Phe Gly Ser His Leu His Lys
275 280 285
Val Cys Glu Arg Glu Asn Ser Thr Val Pro Trp Phe Val Lys Gln
290 295 300
Cys Ile Glu Ala Val Glu Lys Arg Gly Leu Asp Val Asp Gly Ile
305 310 315
Tyr Arg Val Ser Gly Asn Leu Ala Thr Ile Gln Lys Leu Arg Phe
320 325 330
Ile Val Asn Gln Glu Glu Lys Leu Asn Leu Asp Asp Ser Gln Trp
335 340 345
Glu Asp Ile His Val Val Thr Gly Ala Leu Lys Met Phe Phe Arg

```
                    350                 355                 360
Glu Leu Pro Glu Pro Leu Phe Pro Tyr Ser Phe Phe Glu Gln Phe
                    365                 370                 375
Val Glu Ala Ile Lys Lys Gln Asp Asn Asn Thr Arg Ile Glu Ala
                    380                 385                 390
Val Lys Ser Leu Val Gln Lys Leu Pro Pro Pro Asn Arg Asp Thr
                    395                 400                 405
Met Lys Val Leu Phe Gly His Leu Thr Lys Ile Val Ala Lys Ala
                    410                 415                 420
Ser Lys Asn Leu Met Ser Thr Gln Ser Leu Gly Ile Val Phe Gly
                    425                 430                 435
Pro Thr Leu Leu Arg Ala Glu Asn Glu Thr Gly Asn Met Ala Ile
                    440                 445                 450
His Met Val Tyr Gln Asn Gln Ile Ala Glu Leu Met Leu Ser Glu
                    455                 460                 465
Tyr Ser Lys Ile Phe Gly Ser Glu Glu Asp
                    470                 475
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<210> 20
<211> 368
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 129023CD1

<400> 20

```
Met Ala Asn Glu Asn His Gly Ser Pro Arg Glu Glu Ala Ser Leu
  1               5                  10                  15
Leu Ser His Ser Pro Gly Thr Ser Asn Gln Ser Gln Pro Cys Ser
             20                  25                  30
Pro Lys Pro Ile Arg Leu Val Gln Asp Leu Pro Glu Glu Leu Val
         35                  40                  45
His Ala Gly Trp Glu Lys Cys Trp Ser Arg Arg Glu Asn Arg Pro
     50                  55                  60
Tyr Tyr Phe Asn Arg Phe Thr Asn Gln Ser Leu Trp Glu Met Pro
 65                  70                  75
Val Leu Gly Gln His Asp Val Ile Ser Asp Pro Leu Gly Leu Asn
                 80                  85                  90
Ala Thr Pro Leu Pro Gln Asp Ser Ser Leu Val Glu Thr Pro Pro
             95                 100                 105
Ala Glu Asn Lys Pro Arg Lys Arg Gln Leu Ser Glu Glu Gln Pro
            110                 115                 120
Ser Gly Asn Gly Val Lys Lys Pro Lys Ile Glu Ile Pro Val Thr
        125                 130                 135
Pro Thr Gly Gln Ser Val Pro Ser Ser Pro Ser Ile Pro Gly Thr
    140                 145                 150
Pro Thr Leu Lys Met Trp Gly Thr Ser Pro Glu Asp Lys Gln Gln
155                 160                 165
Ala Ala Leu Leu Arg Pro Thr Glu Val Tyr Trp Asp Leu Asp Ile
            170                 175                 180
Gln Thr Asn Ala Val Ile Lys His Arg Gly Pro Ser Glu Val Leu
        185                 190                 195
Pro Pro His Pro Glu Val Glu Leu Leu Arg Ser Gln Leu Ile Leu
    200                 205                 210
Lys Leu Arg Gln His Tyr Arg Glu Leu Cys Gln Gln Arg Glu Gly
215                 220                 225
Ile Glu Pro Pro Arg Glu Ser Phe Asn Arg Trp Met Leu Glu Arg
            230                 235                 240
Lys Val Val Asp Lys Gly Ser Asp Pro Leu Leu Pro Ser Asn Cys
        245                 250                 255
Glu Pro Val Val Ser Pro Ser Met Phe Arg Glu Ile Met Asn Asp
    260                 265                 270
Ile Pro Ile Arg Leu Ser Arg Ile Lys Phe Arg Glu Glu Ala Lys
275                 280                 285
Arg Leu Leu Phe Lys Tyr Ala Glu Ala Ala Arg Arg Leu Ile Glu
            290                 295                 300
```

```
                350                 355                 360
Phe Gln Glu Val Glu Asn Phe Phe Thr Phe Leu Lys Asn Ile Asn
                365                 370                 375
Asp Val Asp Thr Ala Leu Ser Phe Tyr His Met Ala Gly Ala Ser
                380                 385                 390
Leu Asp Lys Val Thr Met Gln Gln Val Ala Arg Thr Val Ala Lys
                395                 400                 405
Val Glu Leu Ser Asp His Val Cys Asp Val Val Phe Ala Leu Phe
                410                 415                 420
Asp Cys Asp Gly Asn Gly Glu Leu Ser Asn Lys Glu Phe Val Ser
                425                 430                 435
Ile Met Lys Gln Arg Leu Met Arg Gly Leu Glu Lys Pro Lys Asp
                440                 445                 450
Met Gly Phe Thr Arg Leu Met Gln Ala Met Trp Lys Cys Ala Gln
                455                 460                 465
Glu Thr Ala Trp Asp Phe Ala Leu Pro Lys Gln
                470                 475
<210> 22
<211> 171
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1682320CD1

<400> 22
Met Glu Lys Arg Leu Gln Glu Ala Gln Leu Tyr Lys Glu Glu Gly
  1               5                  10                  15
Asn Gln Arg Tyr Arg Glu Gly Lys Tyr Arg Asp Ala Val Ser Arg
                20                  25                  30
Tyr His Arg Ala Leu Leu Gln Leu Arg Gly Leu Asp Pro Ser Leu
                35                  40                  45
Pro Ser Pro Leu Pro Asn Leu Gly Pro Gln Gly Pro Ala Leu Thr
                50                  55                  60
Pro Glu Gln Glu Asn Ile Leu His Thr Thr Gln Thr Asp Cys Tyr
                65                  70                  75
Asn Asn Leu Ala Ala Cys Leu Leu Gln Met Glu Pro Val Asn Tyr
                80                  85                  90
Glu Arg Val Arg Glu Tyr Ser Gln Lys Val Leu Glu Arg Gln Pro
                95                 100                 105
Asp Asn Ala Lys Ala Leu Tyr Arg Ala Gly Val Ala Phe Phe His
               110                 115                 120
Leu Gln Asp Tyr Asp Gln Ala Arg His Tyr Leu Leu Ala Ala Val
               125                 130                 135
Asn Arg Gln Pro Lys Asp Ala Asn Val Arg Arg Tyr Leu Gln Leu
               140                 145                 150
Thr Gln Ser Glu Leu Ser Ser Tyr His Arg Lys Glu Lys Gln Leu
               155                 160                 165
Tyr Leu Gly Met Phe Gly
               170
<210> 23
<211> 163
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1728263CD1

<400> 23
Met Phe Phe Ser Glu Ala Arg Ala Arg Ser Arg Thr Trp Glu Ala
  1               5                  10                  15
Ser Pro Ser Glu His Arg Lys Trp Val Glu Val Phe Lys Ala Cys
                20                  25                  30
Asp Glu Asp His Lys Gly Tyr Leu Ser Arg Glu Asp Phe Lys Thr
                35                  40                  45
```

```
Ala Val Val Met Leu Phe Gly Tyr Lys Pro Ser Lys Ile Glu Val
                 50                  55                  60
Asp Ser Val Met Ser Ser Ile Asn Pro Asn Thr Ser Gly Ile Leu
                 65                  70                  75
Leu Glu Gly Phe Leu Asn Ile Val Arg Lys Lys Lys Glu Ala Gln
                 80                  85                  90
Arg Tyr Arg Asn Glu Val Arg His Ile Phe Thr Ala Phe Asp Thr
                 95                 100                 105
Tyr Tyr Arg Gly Phe Leu Thr Leu Glu Asp Phe Lys Lys Ala Phe
                110                 115                 120
Arg Gln Val Ala Pro Lys Leu Pro Glu Arg Thr Val Leu Glu Val
                125                 130                 135
Phe Arg Glu Val Asp Arg Asp Ser Asp Gly His Val Ser Phe Arg
                140                 145                 150
Asp Phe Glu Tyr Ala Leu Asn Tyr Gly Gln Lys Glu Ala
                155                 160
<210> 24
<211> 354
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1867626CD1

<400> 24
Met Gly Glu Gln Pro Ile Phe Ser Thr Arg Ala His Val Phe Gln
  1               5                  10                  15
Ile Asp Pro Asn Thr Lys Lys Asn Trp Val Pro Thr Ser Lys His
                 20                  25                  30
Ala Val Thr Val Ser Tyr Phe Tyr Asp Ser Thr Arg Asn Val Tyr
                 35                  40                  45
Arg Ile Ile Ser Leu Asp Gly Ser Lys Ala Ile Ile Asn Ser Thr
                 50                  55                  60
Ile Thr Pro Asn Met Thr Phe Thr Lys Thr Ser Gln Arg Phe Gly
                 65                  70                  75
Gln Trp Ala Asp Ser Arg Ala Asn Thr Val Tyr Gly Leu Gly Phe
                 80                  85                  90
Ser Ser Glu His His Leu Ser Lys Phe Ala Glu Lys Phe Gln Glu
                 95                 100                 105
Phe Lys Glu Ala Ala Arg Leu Ala Lys Glu Lys Ser Gln Glu Lys
                110                 115                 120
Met Glu Leu Thr Ser Thr Pro Ser Gln Glu Ser Ala Gly Gly Asp
                125                 130                 135
Leu Gln Ser Pro Leu Thr Pro Glu Ser Ile Asn Gly Thr Asp Asp
                140                 145                 150
Glu Arg Thr Pro Asp Val Thr Gln Asn Ser Glu Pro Arg Ala Glu
                155                 160                 165
Pro Thr Gln Asn Ala Leu Pro Phe Ser His Ser Ser Ala Ile Ser
                170                 175                 180
Lys His Trp Glu Ala Glu Leu Ala Thr Leu Lys Gly Asn Asn Ala
                185                 190                 195
Lys Leu Thr Ala Ala Leu Leu Glu Ser Thr Ala Asn Val Lys Gln
                200                 205                 210
Trp Lys Gln Gln Leu Ala Ala Tyr Gln Glu Glu Ala Glu Arg Leu
                215                 220                 225
His Lys Arg Val Thr Glu Leu Glu Cys Val Ser Ser Gln Ala Asn
                230                 235                 240
Ala Val His Thr His Lys Thr Glu Leu Asn Gln Thr Ile Gln Glu
                245                 250                 255
Leu Glu Glu Thr Leu Lys Leu Lys Glu Glu Glu Ile Glu Arg Leu
                260                 265                 270
Lys Gln Glu Ile Asp Asn Ala Arg Glu Leu Gln Glu Gln Arg Asp
                275                 280                 285
Ser Leu Thr Gln Lys Leu Gln Glu Val Glu Ile Arg Asn Lys Asp
                290                 295                 300
Leu Glu Gly Gln Leu Ser Asp Leu Glu Gln Arg Leu Glu Lys Ser
```

```
                    305                 310                 315
Gln Asn Glu Gln Glu Ala Phe Arg Asn Asn Leu Lys Thr Leu Leu
                    320                 325                 330
Glu Ile Leu Asp Gly Lys Ile Phe Glu Leu Thr Glu Leu Arg Asp
                    335                 340                 345
Asn Leu Ala Lys Leu Leu Glu Cys Ser
                    350
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<210> 25
<211> 365
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1990126CD1

<400> 25

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Met Asn Ile Met Asp Phe Asn Val Lys Lys Leu Ala Ala Asp Ala
  1               5                  10                  15
Gly Thr Phe Leu Ser Arg Ala Val Gln Phe Thr Glu Glu Lys Leu
             20                  25                  30
Gly Gln Ala Glu Lys Thr Glu Leu Asp Ala His Leu Glu Asn Leu
         35                  40                  45
Leu Ser Lys Ala Glu Cys Thr Lys Ile Trp Thr Glu Lys Ile Met
     50                  55                  60
Lys Gln Thr Glu Val Leu Leu Gln Pro Asn Pro Asn Ala Arg Ile
 65                  70                  75
Glu Glu Phe Val Tyr Glu Lys Leu Asp Arg Lys Ala Pro Ser Arg
             80                  85                  90
Ile Asn Asn Pro Glu Leu Leu Gly Gln Tyr Met Ile Asp Ala Gly
         95                 100                 105
Thr Glu Phe Gly Pro Gly Thr Ala Tyr Gly Asn Ala Leu Ile Lys
    110                 115                 120
Cys Gly Glu Thr Gln Lys Arg Ile Gly Thr Ala Asp Arg Glu Leu
    125                 130                 135
Ile Gln Thr Ser Ala Leu Asn Phe Leu Thr Pro Leu Arg Asn Phe
    140                 145                 150
Ile Glu Gly Asp Tyr Lys Thr Ile Ala Lys Glu Arg Lys Leu Leu
    155                 160                 165
Gln Asn Lys Arg Leu Asp Leu Asp Ala Ala Lys Thr Arg Leu Lys
    170                 175                 180
Lys Ala Lys Ala Ala Glu Thr Arg Asn Ser Ser Glu Gln Glu Leu
    185                 190                 195
Arg Ile Thr Gln Ser Glu Phe Asp Arg Gln Ala Glu Ile Thr Arg
    200                 205                 210
Leu Leu Leu Glu Gly Ile Ser Ser Thr His Ala His His Leu Arg
    215                 220                 225
Cys Leu Asn Asp Phe Val Glu Ala Gln Met Thr Tyr Tyr Ala Gln
    230                 235                 240
Cys Tyr Gln Tyr Met Leu Asp Leu Gln Lys Gln Leu Gly Ser Phe
    245                 250                 255
Pro Ser Asn Tyr Leu Ser Asn Asn Asn Gln Thr Ser Val Thr Pro
    260                 265                 270
Val Pro Ser Val Leu Pro Asn Ala Ile Gly Ser Ser Ala Met Ala
    275                 280                 285
Ser Thr Ser Gly Leu Val Ile Thr Ser Pro Ser Asn Leu Ser Asp
    290                 295                 300
Leu Lys Glu Cys Ser Gly Ser Arg Lys Ala Arg Val Leu Tyr Asp
    305                 310                 315
Tyr Asp Ala Ala Asn Ser Thr Glu Leu Ser Leu Leu Ala Asp Glu
    320                 325                 330
Val Ile Thr Val Phe Ser Val Val Gly Met Asp Ser Asp Trp Leu
    335                 340                 345
Met Gly Glu Arg Gly Asn Gln Lys Gly Lys Val Pro Ile Thr Tyr
    350                 355                 360
Leu Glu Leu Leu Asn
    365
```

<210> 26
<211> 274
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2104180CD1

<400> 26
Met Ala Thr Thr Val Ser Thr Gln Arg Gly Pro Val Tyr Ile Gly
1 5 10 15
Glu Leu Pro Gln Asp Phe Leu Arg Ile Thr Pro Thr Gln Gln Gln
20 25 30
Arg Gln Val Gln Leu Asp Ala Gln Ala Ala Gln Gln Leu Gln Tyr
35 40 45
Gly Gly Ala Val Gly Thr Val Gly Arg Leu Asn Ile Thr Val Val
50 55 60
Gln Ala Lys Leu Ala Lys Asn Tyr Gly Met Thr Arg Met Asp Pro
65 70 75
Tyr Cys Arg Leu Arg Leu Gly Tyr Ala Val Tyr Glu Thr Pro Thr
80 85 90
Ala His Asn Gly Ala Lys Asn Pro Arg Trp Asn Lys Val Ile His
95 100 105
Cys Thr Val Pro Pro Gly Val Asp Ser Phe Tyr Leu Glu Ile Phe
110 115 120
Asp Glu Arg Ala Phe Ser Met Asp Asp Arg Ile Ala Trp Thr His
125 130 135
Ile Thr Ile Pro Glu Ser Leu Arg Gln Gly Lys Val Glu Asp Lys
140 145 150
Trp Tyr Ser Leu Ser Gly Arg Gln Gly Asp Asp Lys Glu Gly Met
155 160 165
Ile Asn Leu Val Met Ser Tyr Ala Leu Leu Pro Ala Ala Met Val
170 175 180
Met Pro Pro Gln Pro Val Val Leu Met Pro Thr Val Tyr Gln Gln
185 190 195
Gly Val Gly Tyr Val Pro Ile Thr Gly Met Pro Ala Val Cys Ser
200 205 210
Pro Gly Met Val Pro Val Ala Leu Pro Pro Ala Ala Val Asn Ala
215 220 225
Gln Pro Arg Cys Ser Glu Glu Asp Leu Lys Ala Ile Gln Asp Met
230 235 240
Phe Pro Asn Met Asp Gln Glu Val Ile Arg Ser Val Leu Glu Ala
245 250 255
Gln Arg Gly Asn Lys Asp Ala Ala Ile Asn Ser Leu Leu Gln Met
260 265 270
Gly Glu Glu Pro

<210> 27
<211> 129
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2122241CD1

<400> 27
Met Arg Arg Arg Gly Glu Ile Asp Met Ala Thr Glu Gly Asp Val
1 5 10 15
Glu Leu Glu Leu Glu Thr Glu Thr Ser Gly Pro Glu Arg Pro Pro
20 25 30
Glu Lys Pro Arg Lys His Asp Ser Gly Ala Ala Asp Leu Glu Arg
35 40 45
Val Thr Asp Tyr Ala Glu Glu Lys Glu Ile Gln Ser Ser Asn Leu
50 55 60
Glu Thr Ala Met Ser Val Ile Gly Asp Arg Arg Ser Arg Glu Gln

```
                  65                  70                  75
Lys Ala Lys Gln Glu Arg Glu Lys Glu Leu Ala Lys Val Thr Ile
                  80                  85                  90
Lys Lys Glu Asp Leu Glu Leu Ile Met Thr Glu Met Glu Ile Ser
                  95                 100                 105
Arg Ala Ala Ala Glu Arg Ser Leu Arg Glu His Met Gly Asn Val
                 110                 115                 120
Val Glu Ala Leu Ile Ala Leu Thr Asn
                 125
<210> 28
<211> 626
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2580428CD1

<400> 28
Met Gln Arg Ala Asp Ser Glu Gln Pro Ser Lys Arg Pro Arg Cys
  1               5                  10                  15
Asp Asp Ser Pro Arg Thr Pro Ser Asn Thr Pro Ser Ala Glu Ala
                 20                  25                  30
Asp Trp Ser Pro Gly Leu Glu Leu His Pro Asp Tyr Lys Thr Trp
                 35                  40                  45
Gly Pro Glu Gln Val Cys Ser Phe Leu Arg Arg Gly Gly Phe Glu
                 50                  55                  60
Glu Pro Val Leu Leu Lys Asn Ile Arg Glu Asn Glu Ile Thr Gly
                 65                  70                  75
Ala Leu Leu Pro Cys Leu Asp Glu Ser Arg Phe Glu Asn Leu Gly
                 80                  85                  90
Val Ser Ser Leu Gly Glu Arg Lys Lys Leu Leu Ser Tyr Ile Gln
                 95                 100                 105
Arg Leu Val Gln Ile His Val Asp Thr Met Lys Val Ile Asn Asp
                110                 115                 120
Pro Ile His Gly His Ile Glu Leu His Pro Leu Leu Val Arg Ile
                125                 130                 135
Ile Asp Thr Pro Gln Phe Gln Arg Leu Arg Tyr Ile Lys Gln Leu
                140                 145                 150
Gly Gly Gly Tyr Tyr Val Phe Pro Gly Ala Ser His Asn Arg Phe
                155                 160                 165
Glu His Ser Leu Gly Val Gly Tyr Leu Ala Gly Cys Leu Val His
                170                 175                 180
Ala Leu Gly Glu Lys Gln Pro Glu Leu Gln Ile Ser Glu Arg Asp
                185                 190                 195
Val Leu Cys Val Gln Ile Ala Gly Leu Cys His Asp Leu Gly His
                200                 205                 210
Gly Pro Phe Ser His Met Phe Asp Gly Arg Phe Ile Pro Leu Ala
                215                 220                 225
Arg Pro Glu Val Lys Trp Thr His Glu Gln Gly Ser Val Met Met
                230                 235                 240
Phe Glu His Leu Ile Asn Ser Asn Gly Ile Lys Pro Val Met Glu
                245                 250                 255
Gln Tyr Gly Leu Ile Pro Glu Glu Asp Ile Cys Phe Ile Lys Glu
                260                 265                 270
Gln Ile Val Gly Pro Leu Glu Ser Pro Val Glu Asp Ser Leu Trp
                275                 280                 285
Pro Tyr Lys Gly Arg Pro Glu Asn Lys Ser Phe Leu Tyr Glu Ile
                290                 295                 300
Val Ser Asn Lys Arg Asn Gly Ile Asp Val Asp Lys Trp Asp Tyr
                305                 310                 315
Phe Ala Arg Asp Cys His His Leu Gly Ile Gln Asn Asn Phe Asp
                320                 325                 330
Tyr Lys Arg Phe Ile Lys Phe Ala Arg Val Cys Glu Val Asp Asn
                335                 340                 345
Glu Leu Arg Ile Cys Ala Arg Asp Lys Glu Val Gly Asn Leu Tyr
                350                 355                 360
```

```
Asp Met Phe His Thr Arg Asn Ser Leu His Arg Arg Ala Tyr Gln
                365                 370                 375
His Lys Val Gly Asn Ile Ile Asp Thr Met Ile Thr Asp Ala Phe
                380                 385                 390
Leu Lys Ala Asp Asp Tyr Ile Glu Ile Thr Gly Ala Gly Gly Lys
                395                 400                 405
Lys Tyr Arg Ile Ser Thr Ala Ile Asp Asp Met Glu Ala Tyr Thr
                410                 415                 420
Lys Leu Thr Asp Asn Ile Phe Leu Glu Ile Leu Tyr Ser Thr Asp
                425                 430                 435
Pro Lys Leu Lys Asp Ala Arg Glu Ile Leu Lys Gln Ile Glu Tyr
                440                 445                 450
Arg Asn Leu Phe Lys Tyr Val Gly Glu Thr Gln Pro Thr Gly Gln
                455                 460                 465
Ile Lys Ile Lys Arg Glu Asp Tyr Glu Ser Leu Pro Lys Glu Val
                470                 475                 480
Ala Ser Ala Lys Pro Lys Val Leu Leu Asp Val Lys Leu Lys Ala
                485                 490                 495
Glu Asp Phe Ile Val Asp Val Ile Asn Met Asp Tyr Gly Met Gln
                500                 505                 510
Glu Lys Asn Pro Ile Asp His Val Ser Phe Tyr Cys Lys Thr Ala
                515                 520                 525
Pro Asn Arg Ala Ile Arg Ile Thr Lys Asn Gln Val Ser Gln Leu
                530                 535                 540
Leu Pro Glu Lys Phe Ala Glu Gln Leu Ile Arg Val Tyr Cys Lys
                545                 550                 555
Lys Val Asp Arg Lys Ser Leu Tyr Ala Ala Arg Gln Tyr Phe Val
                560                 565                 570
Gln Trp Cys Ala Asp Arg Asn Phe Thr Lys Pro Gln Asp Gly Asp
                575                 580                 585
Val Ile Ala Pro Leu Ile Thr Pro Gln Lys Lys Glu Trp Asn Asp
                590                 595                 600
Ser Thr Ser Val Gln Asn Pro Thr Arg Leu Arg Glu Ala Ser Lys
                605                 610                 615
Ser Arg Val Gln Leu Phe Lys Asp Asp Pro Met
                620                 625
```

<210> 29
<211> 157
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3397189CD1

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<400> 29
Met Ala Pro Lys Lys Leu Ser Cys Leu Arg Ser Leu Leu Leu Pro
  1               5                  10                  15
Leu Ser Leu Thr Leu Leu Leu Pro Gln Ala Asp Thr Arg Ser Phe
                20                  25                  30
Val Val Asp Arg Gly His Asp Arg Phe Leu Leu Asp Gly Ala Pro
                35                  40                  45
Phe Arg Tyr Val Ser Gly Ser Leu His Tyr Phe Arg Val Pro Arg
                50                  55                  60
Val Leu Trp Ala Asp Arg Leu Leu Lys Met Arg Trp Ser Gly Leu
                65                  70                  75
Asn Ala Ile Gln Phe Tyr Val Pro Trp Asn Tyr His Glu Pro Gln
                80                  85                  90
Pro Gly Val Tyr Asn Phe Asn Gly Ser Arg Asp Leu Ile Ala Phe
                95                 100                 105
Leu Asn Glu Ala Ala Leu Ala Asn Leu Leu Val Ile Leu Arg Pro
               110                 115                 120
Gly Pro Tyr Ile Cys Ala Glu Trp Glu Met Gly Gly Leu Pro Ser
               125                 130                 135
Trp Leu Leu Arg Lys Pro Glu Ile His Leu Arg Thr Ser Asp Pro
               140                 145                 150
Gly Glu Leu Arg Gln Arg Ile
```

155

<210> 30
<211> 383
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 4881249CD1

<400> 30
Met Leu Ser Arg Lys Lys Thr Lys Asn Glu Val Ser Lys Pro Ala
1 5 10 15
Glu Val Gln Gly Lys Tyr Val Lys Lys Glu Thr Ser Pro Leu Leu
20 25 30
Arg Asn Leu Met Pro Ser Phe Ile Arg His Gly Pro Thr Ile Pro
35 40 45
Arg Arg Thr Asp Ile Cys Leu Pro Asp Ser Ser Pro Asn Ala Phe
50 55 60
Ser Thr Ser Gly Asp Val Val Ser Arg Asn Gln Ser Phe Leu Arg
65 70 75
Thr Pro Ile Gln Arg Thr Pro His Glu Ile Met Arg Arg Glu Ser
80 85 90
Asn Arg Leu Ser Ala Pro Ser Tyr Leu Ala Arg Ser Leu Ala Asp
95 100 105
Val Pro Arg Glu Tyr Gly Ser Ser Gln Ser Phe Val Thr Glu Val
110 115 120
Ser Phe Ala Val Glu Asn Gly Asp Ser Gly Ser Arg Tyr Tyr Tyr
125 130 135
Ser Asp Asn Phe Phe Asp Gly Gln Arg Lys Arg Pro Leu Gly Asp
140 145 150
Arg Ala His Glu Asp Tyr Arg Tyr Tyr Glu Tyr Asn His Asp Leu
155 160 165
Phe Gln Arg Met Pro Gln Asn Gln Gly Arg His Ala Ser Gly Ile
170 175 180
Gly Arg Val Ala Ala Thr Ser Leu Gly Asn Leu Thr Asn His Gly
185 190 195
Ser Glu Asp Leu Pro Leu Pro Pro Gly Trp Ser Val Asp Trp Thr
200 205 210
Met Arg Gly Arg Lys Tyr Tyr Ile Asp His Asn Thr Asn Thr Thr
215 220 225
His Trp Ser His Pro Leu Glu Arg Glu Gly Leu Pro Pro Gly Trp
230 235 240
Glu Arg Val Glu Ser Ser Glu Phe Gly Thr Tyr Tyr Val Asp His
245 250 255
Thr Asn Lys Lys Ala Gln Tyr Arg His Pro Cys Ala Pro Ser Val
260 265 270
Pro Arg Tyr Asp Gln Pro Pro Pro Val Thr Tyr Gln Pro Gln Gln
275 280 285
Thr Glu Arg Asn Gln Ser Leu Leu Val Pro Ala Asn Pro Tyr His
290 295 300
Thr Ala Glu Ile Pro Asp Trp Leu Gln Val Tyr Ala Arg Ala Pro
305 310 315
Val Lys Tyr Asp His Ile Leu Lys Trp Glu Leu Phe Gln Leu Ala
320 325 330
Asp Leu Asp Thr Tyr Gln Gly Met Leu Lys Leu Leu Phe Met Lys
335 340 345
Glu Leu Glu Gln Ile Val Lys Met Tyr Glu Ala Tyr Arg Gln Ala
350 355 360
Leu Leu Thr Glu Leu Glu Asn Arg Lys Gln Arg Gln Gln Trp Tyr
365 370 375
Ala Gln Gln His Gly Lys Asn Phe
380

<210> 31
<211> 478
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 431871CD1

<400> 31

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Met Asp Thr Ser Asp Leu Phe Ala Ser Cys Arg Lys Gly Asp Val
  1               5                  10                  15
Gly Arg Val Arg Tyr Leu Leu Glu Gln Arg Asp Val Glu Val Asn
             20                  25                  30
Val Arg Asp Lys Trp Asp Ser Thr Pro Leu Tyr Tyr Ala Cys Leu
         35                  40                  45
Cys Gly His Glu Glu Leu Val Leu Tyr Leu Leu Ala Asn Gly Ala
     50                  55                  60
Arg Cys Glu Ala Asn Thr Phe Asp Gly Glu Arg Cys Leu Tyr Gly
 65                  70                  75
Ala Leu Ser Asp Pro Ile Arg Arg Ala Leu Arg Asp Tyr Lys Gln
             80                  85                  90
Val Thr Ala Ser Cys Arg Arg Arg Asp Tyr Tyr Asp Asp Phe Leu
         95                 100                 105
Gln Arg Leu Leu Glu Gln Gly Ile His Ser Asp Val Val Phe Val
    110                 115                 120
Val His Gly Lys Pro Phe Arg Val His Arg Cys Val Leu Gly Ala
125                 130                 135
Arg Ser Ala Tyr Phe Ala Asn Met Leu Asp Thr Lys Trp Lys Gly
140                 145                 150
Lys Ser Val Val Val Leu Arg His Pro Leu Ile Asn Pro Val Ala
155                 160                 165
Phe Gly Ala Leu Leu Gln Tyr Leu Tyr Thr Gly Arg Leu Asp Ile
170                 175                 180
Gly Val Glu His Val Ser Asp Cys Glu Arg Leu Ala Lys Gln Cys
185                 190                 195
Gln Leu Trp Asp Leu Leu Ser Asp Leu Glu Ala Lys Cys Glu Lys
200                 205                 210
Val Ser Glu Phe Val Ala Ser Lys Pro Gly Thr Cys Val Lys Val
215                 220                 225
Leu Thr Ile Glu Pro Pro Pro Ala Asp Pro Arg Leu Arg Glu Asp
230                 235                 240
Met Ala Leu Leu Ala Asp Cys Ala Leu Pro Pro Glu Leu Arg Gly
245                 250                 255
Asp Leu Trp Glu Leu Pro Phe Pro Cys Pro Asp Gly Phe Asn Ser
260                 265                 270
Cys Pro Asp Ile Cys Phe Arg Val Ala Gly Cys Ser Phe Leu Cys
275                 280                 285
His Lys Ala Phe Phe Cys Gly Arg Ser Asp Tyr Phe Arg Ala Leu
290                 295                 300
Leu Asp Asp His Phe Arg Glu Ser Glu Glu Pro Ala Thr Ser Gly
305                 310                 315
Gly Pro Pro Ala Val Thr Leu His Gly Ile Ser Pro Asp Val Phe
320                 325                 330
Thr His Val Leu Tyr Tyr Met Tyr Ser Asp His Thr Glu Leu Ser
335                 340                 345
Pro Glu Ala Ala Tyr Asp Val Leu Ser Val Ala Asp Met Tyr Leu
350                 355                 360
Leu Pro Gly Leu Lys Arg Leu Cys Gly Arg Ser Leu Ala Gln Met
365                 370                 375
Leu Asp Glu Asp Thr Val Val Gly Val Trp Arg Val Ala Lys Leu
380                 385                 390
Phe Arg Leu Ala Arg Leu Glu Asp Gln Cys Thr Glu Tyr Met Ala
395                 400                 405
Lys Val Ile Glu Lys Leu Val Glu Arg Glu Asp Phe Val Glu Ala
410                 415                 420
Val Lys Glu Glu Ala Ala Ala Val Ala Ala Arg Gln Glu Thr Asp
425                 430                 435
Ser Ile Pro Leu Val Asp Asp Ile Arg Phe His Val Ala Ser Thr
440                 445                 450
Val Gln Thr Tyr Ser Ala Ile Glu Glu Ala Gln Gln Arg Leu Arg
455                 460                 465
```

Ala Leu Glu Asp Leu Leu Val Ser Ile Gly Leu Asp Cys
470 475

<210> 32
<211> 275
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 526155CD1

<400> 32
Met Ser Ala Glu Val Lys Val Thr Gly Gln Asn Gln Glu Gln Phe
1 5 10 15
Leu Leu Leu Ala Lys Ser Ala Lys Gly Ala Ala Leu Ala Thr Leu
20 25 30
Ile His Gln Val Leu Glu Ala Pro Gly Val Tyr Val Phe Gly Glu
35 40 45
Leu Leu Asp Met Pro Asn Val Arg Glu Leu Ala Glu Ser Asp Phe
50 55 60
Ala Ser Thr Phe Arg Leu Leu Thr Val Phe Ala Tyr Gly Thr Tyr
65 70 75
Ala Asp Tyr Leu Ala Glu Ala Arg Asn Leu Pro Pro Leu Thr Glu
80 85 90
Ala Gln Lys Asn Lys Leu Arg His Leu Ser Val Val Thr Leu Ala
95 100 105
Ala Lys Val Lys Cys Ile Pro Tyr Ala Val Leu Leu Glu Ala Leu
110 115 120
Ala Leu Arg Asn Val Arg Gln Leu Glu Asp Leu Val Ile Glu Ala
125 130 135
Val Tyr Ala Asp Val Leu Arg Gly Ser Leu Asp Gln Arg Asn Gln
140 145 150
Arg Leu Glu Val Asp Tyr Ser Ile Gly Arg Asp Ile Gln Arg Gln
155 160 165
Asp Leu Ser Ala Ile Ala Arg Thr Leu Gln Glu Trp Cys Val Gly
170 175 180
Cys Glu Val Val Leu Ser Gly Ile Glu Glu Gln Val Ser Arg Ala
185 190 195
Asn Gln His Lys Glu Gln Gln Leu Gly Leu Lys Gln Gln Ile Glu
200 205 210
Ser Glu Val Ala Asn Leu Lys Lys Thr Ile Lys Val Thr Thr Ala
215 220 225
Ala Ala Ala Ala Ala Thr Ser Gln Asp Pro Glu Gln His Leu Thr
230 235 240
Glu Leu Arg Glu Pro Ala Pro Gly Thr Asn Gln Arg Gln Pro Ser
245 250 255
Lys Lys Ala Ser Lys Gly Lys Gly Leu Arg Gly Ser Ala Lys Ile
260 265 270
Trp Ser Lys Ser Asn
275

<210> 33
<211> 217
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 676234CD1

<400> 33
Met Ala Ser Thr Gly Leu Glu Leu Leu Gly Met Thr Leu Ala Val
1 5 10 15
Leu Gly Trp Leu Gly Thr Leu Val Ser Cys Ala Leu Pro Leu Trp
20 25 30
Lys Val Thr Ala Phe Ile Gly Asn Ser Ile Val Val Ala Gln Val

```
                    35                  40                  45
Val Trp Glu Gly Leu Trp Met Ser Cys Val Val Gln Ser Thr Gly
                    50                  55                  60
Gln Met Gln Cys Lys Val Tyr Asp Ser Leu Leu Ala Leu Pro Gln
                    65                  70                  75
Asp Leu Gln Ala Ala Arg Ala Leu Cys Val Ile Ala Leu Leu Leu
                    80                  85                  90
Ala Leu Leu Gly Leu Leu Val Ala Ile Thr Gly Ala Gln Cys Thr
                    95                 100                 105
Thr Cys Val Glu Asp Glu Gly Ala Lys Ala Arg Ile Val Leu Thr
                   110                 115                 120
Ala Gly Val Ile Leu Leu Leu Ala Gly Ile Leu Val Leu Ile Pro
                   125                 130                 135
Val Cys Trp Thr Ala His Ala Ile Ile Gln Asp Phe Tyr Asn Pro
                   140                 145                 150
Leu Val Ala Glu Ala Leu Lys Arg Glu Leu Gly Ala Ser Leu Tyr
                   155                 160                 165
Leu Gly Trp Ala Ala Ala Ala Leu Leu Met Leu Gly Gly Gly Leu
                   170                 175                 180
Leu Cys Cys Thr Cys Pro Pro Pro Gln Val Glu Arg Pro Arg Gly
                   185                 190                 195
Pro Arg Leu Gly Tyr Ser Ile Pro Ser Arg Ser Gly Ala Ser Gly
                   200                 205                 210
Leu Asp Lys Arg Asp Tyr Val
                   215
<210> 34
<211> 74
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 720145CD1

<400> 34
Met Asp Asp Tyr Thr Ser Ala Ile Glu Val Gln Pro Asn Phe Glu
  1               5                  10                  15
Val Pro Tyr Tyr Asn Arg Gly Leu Ile Leu Tyr Arg Leu Gly Tyr
                20                  25                  30
Phe Asp Asp Ala Leu Glu Asp Phe Lys Lys Val Leu Asp Leu Asn
                35                  40                  45
Pro Gly Phe Gln Asp Ala Thr Leu Ser Leu Lys Gln Thr Ile Leu
                50                  55                  60
Asp Lys Glu Glu Lys Gln Arg Arg Asn Val Ala Lys Asn Tyr
                65                  70
<210> 35
<211> 367
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1001951CD1

<400> 35
Met Val Gln Gln Phe Leu Arg Gln Ala Gln Arg Gly Thr Glu Glu
  1               5                  10                  15
Lys Glu Arg Glu Gly Ala Leu Val Ser Leu Arg Arg Gly Leu Gln
                20                  25                  30
His Pro Glu Thr Gln Gln Thr Phe Ile Arg Ser Cys Val Cys Ile
                35                  40                  45
His Trp Val Thr Leu Ile Val Glu Ser Glu Ala Val Arg Arg Gln
                50                  55                  60
Leu Leu Pro Gln Gly Ile Val Pro Ala Leu Ala Ala Cys Ile Gln
                65                  70                  75
Ser Pro His Val Ala Val Leu Glu Ala Leu Gly Tyr Ala Leu Ser
                80                  85                  90
```

```
Gln Leu Leu Gln Ala Glu Glu Ala Pro Glu Lys Ile Ile Pro Ser
                95                  100                 105
Ile Leu Ala Ser Thr Leu Pro Gln His Met Leu Gln Met Leu Gln
            110                 115                 120
Pro Gly Pro Lys Leu Asn Pro Gly Val Ala Val Glu Phe Ala Trp
            125                 130                 135
Cys Leu His Tyr Ile Ile Cys Ser Gln Val Ser Asn Pro Leu Leu
            140                 145                 150
Ile Gly His Gly Ala Leu Ser Thr Leu Gly Leu Leu Leu Leu Asp
            155                 160                 165
Leu Ala Gly Ala Val Gln Lys Thr Glu Asp Ala Gly Leu Glu Leu
            170                 175                 180
Leu Ala Cys Pro Val Leu Arg Cys Leu Ser Asn Leu Leu Thr Glu
            185                 190                 195
Ala Ala Val Glu Thr Val Gly Gly Gln Met Gln Leu Arg Asp Glu
            200                 205                 210
Arg Val Val Ala Ala Leu Phe Ile Leu Leu Gln Phe Phe Phe Gln
            215                 220                 225
Lys Gln Pro Ser Leu Leu Pro Glu Gly Leu Trp Leu Leu Asn Asn
            230                 235                 240
Leu Thr Ala Asn Ser Pro Ser Phe Cys Thr Ser Leu Leu Ser Leu
            245                 250                 255
Asp Leu Ile Glu Pro Leu Leu Gln Leu Leu Pro Val Ser Asn Val
            260                 265                 270
Val Ser Val Met Val Leu Thr Val Leu Cys Asn Val Ala Glu Lys
            275                 280                 285
Gly Pro Ala Tyr Cys Gln Arg Leu Trp Pro Gly Pro Leu Leu Pro
            290                 295                 300
Ala Leu Leu His Thr Leu Ala Phe Ser Asp Thr Glu Val Val Gly
            305                 310                 315
Gln Ser Leu Glu Leu Leu His Leu Leu Phe Leu Tyr Gln Pro Glu
            320                 325                 330
Ala Val Gln Val Phe Leu Gln Gln Ser Gly Leu Gln Ala Trp Lys
            335                 340                 345
Arg His Gln Glu Glu Ala Gln Leu Gln Asp Arg Val Tyr Ala Leu
            350                 355                 360
Gln Gln Thr Ala Leu Gln Gly
            365
```

<210> 36
<211> 1113
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1243349CD1

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<400> 36
Met Ile Ala Val Ser Phe Lys Cys Arg Cys Gln Ile Leu Arg Arg
  1               5                  10                  15
Leu Thr Lys Asp Glu Ser Pro Tyr Thr Lys Ser Ala Ser Gln Thr
            20                  25                  30
Lys Pro Pro Asp Gly Ala Leu Ala Val Arg Arg Gln Ser Ile Pro
            35                  40                  45
Glu Glu Phe Lys Gly Ser Thr Val Val Glu Leu Met Lys Lys Glu
            50                  55                  60
Gly Thr Thr Leu Gly Leu Thr Val Ser Gly Gly Ile Asp Lys Asp
            65                  70                  75
Gly Lys Pro Arg Val Ser Asn Leu Arg Gln Gly Gly Ile Ala Ala
            80                  85                  90
Arg Ser Asp Gln Leu Asp Val Gly Asp Tyr Ile Lys Ala Val Asn
            95                 100                 105
Gly Ile Asn Leu Ala Lys Phe Arg His Asp Glu Ile Ile Ser Leu
            110                 115                 120
Leu Lys Asn Val Gly Glu Arg Val Val Leu Glu Val Glu Tyr Glu
            125                 130                 135
Leu Pro Pro Val Ser Val Gln Gly Ser Ser Val Ile Phe Arg Thr
```

```
                    140                 145                 150
Val Glu Val Thr Leu His Lys Glu Gly Asn Thr Phe Gly Phe Val
                155                 160                 165
Ile Arg Gly Gly Ala His Asp Asp Arg Asn Lys Ser Arg Pro Val
                170                 175                 180
Val Ile Thr Cys Val Arg Pro Gly Gly Pro Ala Asp Arg Glu Gly
                185                 190                 195
Thr Ile Lys Pro Gly Asp Arg Leu Leu Ser Val Asp Gly Ile Arg
                200                 205                 210
Leu Leu Gly Thr Thr His Ala Glu Ala Met Ser Ile Leu Lys Gln
                215                 220                 225
Cys Gly Gln Glu Ala Ala Leu Leu Ile Glu Tyr Asp Val Ser Val
                230                 235                 240
Met Asp Ser Val Ala Thr Ala Ser Gly Pro Leu Leu Val Glu Val
                245                 250                 255
Ala Lys Thr Pro Gly Ala Ser Leu Gly Val Ala Leu Thr Thr Ser
                260                 265                 270
Met Cys Cys Asn Lys Gln Val Ile Val Ile Asp Lys Ile Lys Ser
                275                 280                 285
Ala Ser Ile Ala Asp Arg Cys Gly Ala Leu His Val Gly Asp His
                290                 295                 300
Ile Leu Ser Ile Asp Gly Thr Ser Met Glu Tyr Cys Thr Leu Ala
                305                 310                 315
Glu Ala Thr Gln Phe Leu Ala Asn Thr Thr Asp Gln Val Lys Leu
                320                 325                 330
Glu Ile Leu Pro His His Gln Thr Arg Leu Ala Leu Lys Gly Pro
                335                 340                 345
Asp His Val Lys Ile Gln Arg Ser Asp Arg Gln Leu Thr Trp Asp
                350                 355                 360
Ser Trp Ala Ser Asn His Ser Ser Leu His Thr Asn His His Tyr
                365                 370                 375
Asn Thr Tyr His Pro Asp His Cys Arg Val Pro Ala Leu Thr Phe
                380                 385                 390
Pro Lys Ala Pro Pro Pro Asn Ser Pro Pro Ala Leu Val Ser Ser
                395                 400                 405
Ser Phe Ser Pro Thr Ser Met Ser Ala Tyr Ser Leu Ser Ser Leu
                410                 415                 420
Asn Met Gly Thr Leu Pro Arg Ser Leu Tyr Ser Thr Ser Pro Arg
                425                 430                 435
Gly Thr Met Met Arg Arg Arg Leu Lys Lys Lys Asp Phe Lys Ser
                440                 445                 450
Ser Leu Ser Leu Ala Ser Ser Thr Val Gly Leu Ala Gly Gln Val
                455                 460                 465
Val His Thr Glu Thr Thr Glu Val Val Leu Thr Ala Asp Pro Val
                470                 475                 480
Thr Gly Phe Gly Ile Gln Leu Gln Gly Ser Val Phe Ala Thr Glu
                485                 490                 495
Thr Leu Ser Ser Pro Pro Leu Ile Ser Tyr Ile Glu Ala Asp Ser
                500                 505                 510
Pro Ala Glu Arg Cys Gly Val Leu Gln Ile Gly Asp Arg Val Met
                515                 520                 525
Ala Ile Asn Gly Ile Pro Thr Glu Asp Ser Thr Phe Glu Glu Ala
                530                 535                 540
Ser Gln Leu Leu Arg Asp Ser Ser Ile Thr Ser Lys Val Thr Leu
                545                 550                 555
Glu Ile Glu Phe Asp Val Ala Glu Ser Val Ile Pro Ser Ser Gly
                560                 565                 570
Thr Phe His Val Lys Leu Pro Lys Lys His Asn Val Glu Leu Gly
                575                 580                 585
Ile Thr Ile Ser Ser Pro Ser Ser Arg Lys Pro Gly Asp Pro Leu
                590                 595                 600
Val Ile Ser Asp Ile Lys Lys Gly Ser Val Ala His Arg Thr Gly
                605                 610                 615
Thr Leu Glu Leu Gly Asp Lys Leu Leu Ala Ile Asp Asn Ile Arg
                620                 625                 630
Leu Asp Asn Cys Ser Met Glu Asp Ala Val Gln Ile Leu Gln Gln
                635                 640                 645
```

Cys Glu Asp Leu Val Lys Leu Lys Ile Arg Lys Asp Glu Asp Asn
650 655 660
Ser Asp Glu Gln Glu Ser Ser Gly Ala Ile Ile Tyr Thr Val Glu
665 670 675
Leu Lys Arg Tyr Gly Gly Pro Leu Gly Ile Thr Ile Ser Gly Thr
680 685 690
Glu Glu Pro Phe Asp Pro Ile Ile Ile Ser Ser Leu Thr Lys Gly
695 700 705
Gly Leu Ala Glu Arg Thr Gly Ala Ile His Ile Gly Asp Arg Ile
710 715 720
Leu Ala Ile Asn Ser Ser Ser Leu Lys Gly Lys Pro Leu Ser Glu
725 730 735
Ala Ile His Leu Leu Gln Met Ala Gly Glu Thr Val Thr Leu Lys
740 745 750
Ile Lys Lys Gln Thr Asp Ala Gln Ser Ala Ser Ser Pro Lys Lys
755 760 765
Phe Pro Ile Ser Ser His Leu Ser Asp Leu Gly Asp Val Glu Glu
770 775 780
Asp Ser Ser Pro Ala Gln Lys Pro Gly Lys Leu Ser Asp Met Tyr
785 790 795
Pro Ser Thr Val Pro Ser Val Asp Ser Ala Val Asp Ser Trp Asp
800 805 810
Gly Ser Ala Ile Asp Thr Ser Tyr Gly Thr Glu Gly Thr Ser Phe
815 820 825
Gln Ala Ser Gly Tyr Asn Phe Asn Thr Tyr Asp Trp Arg Ser Pro
830 835 840
Lys Gln Arg Gly Ser Leu Ser Pro Val Thr Lys Pro Arg Ser Gln
845 850 855
Thr Tyr Pro Asp Val Gly Leu Ser Tyr Glu Asp Trp Asp Arg Ser
860 865 870
Thr Ala Ser Gly Phe Ala Gly Ala Ala Asp Ser Ala Glu Thr Glu
875 880 885
Gln Glu Glu Asn Phe Trp Ser Gln Ala Leu Glu Asp Leu Glu Thr
890 895 900
Cys Gly Gln Ser Gly Ile Leu Arg Glu Leu Glu Ala Thr Ile Met
905 910 915
Ser Gly Ser Thr Met Ser Leu Asn His Glu Ala Pro Thr Pro Arg
920 925 930
Ser Gln Leu Gly Arg Gln Ala Ser Phe Gln Glu Arg Ser Ser Ser
935 940 945
Arg Pro His Tyr Ser Gln Thr Thr Arg Ser Asn Thr Leu Pro Ser
950 955 960
Asp Val Gly Arg Lys Ser Val Thr Leu Arg Lys Met Lys Gln Glu
965 970 975
Ile Lys Glu Ile Met Ser Pro Thr Pro Val Glu Leu His Lys Val
980 985 990
Thr Leu Tyr Lys Asp Ser Asp Met Glu Asp Phe Gly Phe Ser Val
995 1000 1005
Ala Asp Gly Leu Leu Glu Lys Gly Val Tyr Val Lys Asn Ile Arg
1010 1015 1020
Pro Ala Gly Pro Gly Asp Leu Gly Gly Leu Lys Pro Tyr Asp Arg
1025 1030 1035
Leu Leu Gln Val Asn His Val Arg Thr Arg Asp Phe Asp Cys Cys
1040 1045 1050
Leu Val Val Pro Leu Ile Ala Glu Ser Gly Asn Lys Leu Asp Leu
1055 1060 1065
Val Ile Ser Arg Asn Pro Leu Ala Ser Gln Lys Ser Ile Asp Gln
1070 1075 1080
Gln Ser Leu Pro Gly Asp Trp Ser Glu Gln Asn Ser Ala Phe Phe
1085 1090 1095
Gln Gln Pro Ser His Gly Gly Asn Leu Glu Thr Arg Glu Pro Thr
1100 1105 1110
Asn Thr Leu

<210> 37
<211> 511
<212> PRT

<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1338201CD1

<400> 37
Met Ser Arg Gly Pro Glu Glu Val Asn Arg Leu Thr Glu Ser Thr
1 5 10 15
Tyr Arg Asn Val Met Glu Gln Phe Asn Pro Gly Leu Arg Asn Leu
20 25 30
Ile Asn Leu Gly Lys Asn Tyr Glu Lys Ala Val Asn Ala Met Ile
35 40 45
Leu Ala Gly Lys Ala Tyr Tyr Asp Gly Val Ala Lys Ile Gly Glu
50 55 60
Ile Ala Thr Gly Ser Pro Val Ser Thr Glu Leu Gly His Val Leu
65 70 75
Ile Glu Ile Ser Ser Thr His Lys Lys Leu Asn Glu Ser Leu Asp
80 85 90
Glu Asn Phe Lys Lys Phe His Lys Glu Ile Ile His Glu Leu Glu
95 100 105
Lys Lys Ile Glu Leu Asp Val Lys Tyr Met Asn Ala Thr Leu Lys
110 115 120
Arg Tyr Gln Thr Glu His Lys Asn Lys Leu Glu Ser Leu Glu Lys
125 130 135
Ser Gln Ala Glu Leu Lys Lys Ile Arg Arg Lys Ser Gln Gly Ser
140 145 150
Arg Asn Ala Leu Lys Tyr Glu His Lys Glu Ile Glu Tyr Val Glu
155 160 165
Thr Val Thr Ser Arg Gln Ser Glu Ile Gln Lys Phe Ile Ala Asp
170 175 180
Gly Cys Lys Glu Ala Leu Leu Glu Glu Lys Arg Arg Phe Cys Phe
185 190 195
Leu Val Asp Lys His Cys Gly Phe Ala Asn His Ile His Tyr Tyr
200 205 210
His Leu Gln Ser Ala Glu Leu Leu Asn Ser Lys Leu Pro Arg Trp
215 220 225
Gln Glu Thr Cys Val Asp Ala Ile Lys Val Pro Glu Lys Ile Met
230 235 240
Asn Met Ile Glu Glu Ile Lys Thr Pro Ala Ser Thr Pro Val Ser
245 250 255
Gly Thr Pro Gln Ala Ser Pro Met Ile Glu Arg Ser Asn Val Val
260 265 270
Arg Lys Asp Tyr Asp Thr Leu Ser Lys Cys Ser Pro Lys Met Pro
275 280 285
Pro Ala Pro Ser Gly Arg Ala Tyr Thr Ser Pro Leu Ile Asp Met
290 295 300
Phe Asn Asn Pro Ala Thr Ala Ala Pro Asn Ser Gln Arg Val Asn
305 310 315
Asn Ser Thr Gly Thr Ser Glu Asp Pro Ser Leu Gln Arg Ser Val
320 325 330
Ser Val Ala Thr Gly Leu Asn Met Met Lys Lys Gln Lys Val Lys
335 340 345
Thr Ile Phe Pro His Thr Ala Gly Ser Asn Lys Thr Leu Leu Ser
350 355 360
Phe Ala Gln Gly Asp Val Ile Thr Leu Leu Ile Pro Glu Glu Lys
365 370 375
Asp Gly Trp Leu Tyr Gly Glu His Asp Val Ser Lys Ala Arg Gly
380 385 390
Trp Phe Pro Ser Ser Tyr Thr Lys Leu Leu Glu Glu Asn Glu Thr
395 400 405
Glu Ala Val Thr Val Pro Thr Pro Ser Pro Thr Pro Val Arg Ser
410 415 420
Ile Ser Thr Val Asn Leu Ser Glu Asn Ser Ser Val Val Ile Pro
425 430 435
Pro Pro Asp Tyr Leu Glu Cys Leu Ser Met Gly Ala Ala Ala Asp
440 445 450

```
Arg Arg Ala Asp Ser Ala Arg Thr Thr Ser Thr Phe Lys Ala Pro
                455                 460                 465
Ala Ser Lys Pro Glu Thr Ala Ala Pro Asn Asp Ala Asn Gly Thr
            470                 475                 480
Ala Lys Pro Pro Phe Leu Ser Gly Glu Asn Pro Phe Ala Thr Val
            485                 490                 495
Lys Leu Arg Pro Thr Val Thr Asn Asp Arg Ser Ala Pro Ile Ile
            500                 505                 510
Arg
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<210> 38
<211> 1177
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1405141CD1

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<400> 38
Met Thr Thr Ile Leu Lys Pro Ser Ala Asp Phe Leu Thr Ser Asn
  1               5                  10                  15
Lys Leu Leu Lys Tyr Ser Trp Phe Phe Phe Asp Val Leu Ile Lys
            20                  25                  30
Ser Met Ala Gln His Leu Ile Glu Asn Ser Lys Val Lys Leu Leu
            35                  40                  45
Arg Asn Gln Arg Phe Pro Ala Ser Tyr His His Ala Val Glu Thr
            50                  55                  60
Val Val Asn Met Leu Met Pro His Ile Thr Gln Lys Phe Arg Asp
            65                  70                  75
Asn Pro Glu Ala Ser Lys Asn Ala Asn His Ser Leu Ala Val Phe
            80                  85                  90
Ile Lys Arg Cys Phe Thr Phe Met Asp Arg Gly Phe Val Phe Lys
            95                 100                 105
Gln Ile Asn Asn Tyr Ile Ser Cys Phe Ala Pro Gly Asp Pro Lys
           110                 115                 120
Thr Leu Phe Glu Tyr Lys Phe Glu Phe Leu Arg Val Val Cys Asn
           125                 130                 135
His Glu His Tyr Ile Pro Leu Asn Leu Pro Met Pro Phe Gly Lys
           140                 145                 150
Gly Arg Ile Gln Arg Tyr Gln Asp Leu Gln Leu Asp Tyr Ser Leu
           155                 160                 165
Thr Asp Glu Phe Cys Arg Asn His Phe Leu Val Gly Leu Leu Leu
           170                 175                 180
Arg Glu Val Gly Thr Ala Leu Gln Glu Phe Arg Glu Val Arg Leu
           185                 190                 195
Ile Ala Ile Ser Val Leu Lys Asn Leu Leu Ile Lys His Ser Phe
           200                 205                 210
Asp Asp Arg Tyr Ala Ser Arg Ser His Gln Ala Arg Ile Ala Thr
           215                 220                 225
Leu Tyr Leu Pro Leu Phe Gly Leu Leu Ile Glu Asn Val Gln Arg
           230                 235                 240
Ile Asn Val Arg Asp Val Ser Pro Phe Pro Val Asn Ala Gly Met
           245                 250                 255
Thr Val Lys Asp Glu Ser Leu Ala Leu Pro Ala Val Asn Pro Leu
           260                 265                 270
Val Thr Pro Gln Lys Gly Ser Thr Leu Asp Asn Ser Leu His Lys
           275                 280                 285
Asp Leu Leu Gly Ala Ile Ser Gly Ile Ala Ser Pro Tyr Thr Thr
           290                 295                 300
Ser Thr Pro Asn Ile Asn Ser Val Arg Asn Ala Asp Ser Arg Gly
           305                 310                 315
Ser Leu Ile Ser Thr Asp Ser Gly Asn Ser Leu Pro Glu Arg Asn
           320                 325                 330
Ser Glu Lys Ser Asn Ser Leu Asp Lys His Gln Gln Ser Ser Thr
           335                 340                 345
Leu Gly Asn Ser Val Val Arg Cys Asp Lys Leu Asp Gln Ser Glu
```

```
                350                 355                 360
Ile Lys Ser Leu Leu Met Cys Phe Leu Tyr Ile Leu Lys Ser Met
                365                 370                 375
Ser Asp Asp Ala Leu Phe Thr Tyr Trp Asn Lys Ala Ser Thr Ser
                380                 385                 390
Glu Leu Met Asp Phe Phe Thr Ile Ser Glu Val Cys Leu His Gln
                395                 400                 405
Phe Gln Tyr Met Gly Lys Arg Tyr Ile Ala Ser Val Arg Lys Ile
                410                 415                 420
Ser Ser Val Leu Gly Ile Ser Val Asp Asn Gly Tyr Gly His Ser
                425                 430                 435
Asp Ala Asp Val Leu His Gln Ser Leu Leu Glu Ala Asn Ile Ala
                440                 445                 450
Thr Glu Val Cys Leu Thr Ala Leu Asp Thr Leu Ser Leu Phe Thr
                455                 460                 465
Leu Ala Phe Lys Asn Gln Leu Leu Ala Asp His Gly His Asn Pro
                470                 475                 480
Leu Met Lys Lys Val Phe Asp Val Tyr Leu Cys Phe Leu Gln Lys
                485                 490                 495
His Gln Ser Glu Thr Ala Leu Lys Asn Val Phe Thr Ala Leu Arg
                500                 505                 510
Ser Leu Ile Tyr Lys Phe Pro Ser Thr Phe Tyr Glu Gly Arg Ala
                515                 520                 525
Asp Met Cys Ala Ala Leu Cys Tyr Glu Ile Leu Lys Cys Cys Asn
                530                 535                 540
Ser Lys Leu Ser Ser Ile Arg Thr Glu Ala Ser Gln Leu Leu Tyr
                545                 550                 555
Phe Leu Met Arg Asn Asn Phe Asp Tyr Thr Gly Lys Lys Ser Phe
                560                 565                 570
Val Arg Thr His Leu Gln Val Ile Ile Ser Val Ser Gln Leu Ile
                575                 580                 585
Ala Asp Val Val Gly Ile Gly Gly Thr Arg Phe Gln Gln Ser Leu
                590                 595                 600
Ser Ile Ile Asn Asn Cys Ala Asn Ser Asp Arg Leu Ile Lys His
                605                 610                 615
Thr Ser Phe Ser Ser Asp Val Lys Asp Leu Thr Lys Arg Ile Arg
                620                 625                 630
Thr Val Leu Met Ala Thr Ala Gln Met Lys Glu His Glu Asn Asp
                635                 640                 645
Pro Glu Met Leu Val Asp Leu Gln Tyr Ser Leu Ala Lys Ser Tyr
                650                 655                 660
Ala Ser Thr Pro Glu Leu Arg Lys Thr Trp Leu Asp Ser Met Ala
                665                 670                 675
Arg Ile His Val Lys Asn Gly Asp Leu Ser Glu Ala Ala Met Cys
                680                 685                 690
Tyr Val His Val Thr Ala Leu Val Ala Glu Tyr Leu Thr Arg Lys
                695                 700                 705
Gly Val Phe Arg Gln Gly Cys Thr Ala Phe Arg Val Ile Thr Pro
                710                 715                 720
Asn Ile Asp Glu Glu Ala Ser Met Met Glu Asp Val Gly Met Gln
                725                 730                 735
Asp Val His Phe Asn Glu Asp Val Leu Met Glu Leu Leu Glu Gln
                740                 745                 750
Cys Ala Asp Gly Leu Trp Lys Ala Glu Arg Tyr Glu Leu Ile Ala
                755                 760                 765
Asp Ile Tyr Lys Leu Ile Ile Pro Ile Tyr Glu Lys Arg Arg Asp
                770                 775                 780
Phe Glu Arg Leu Ala His Leu Tyr Asp Thr Leu His Arg Ala Tyr
                785                 790                 795
Ser Lys Val Thr Glu Val Met His Ser Gly Arg Ser Val Leu Gly
                800                 805                 810
Thr Tyr Phe Arg Val Ala Phe Phe Gly Gln Gly Phe Phe Glu Asp
                815                 820                 825
Glu Asp Gly Lys Glu Tyr Ile Tyr Lys Glu Pro Lys Leu Thr Pro
                830                 835                 840
Leu Ser Glu Ile Ser Gln Arg Leu Leu Lys Leu Tyr Ser Asp Lys
                845                 850                 855
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Phe Gly Ser Glu Asn Val Lys Met Ile Gln Asp Ser Gly Lys Val
                860                 865                 870
Asn Pro Lys Asp Leu Asp Ser Lys Tyr Ala Tyr Ile Gln Val Thr
                875                 880                 885
His Val Ile Pro Phe Phe Asp Glu Lys Glu Leu Gln Glu Arg Lys
                890                 895                 900
Thr Glu Phe Glu Arg Ser His Asn Ile Arg Arg Phe Met Phe Glu
                905                 910                 915
Met Pro Phe Thr Gln Thr Gly Lys Arg Gln Gly Gly Val Glu Glu
                920                 925                 930
Gln Cys Lys Arg Arg Thr Ile Leu Thr Ala Ile His Cys Phe Pro
                935                 940                 945
Tyr Val Lys Lys Arg Ile Pro Val Met Tyr Gln His His Thr Asp
                950                 955                 960
Leu Asn Pro Ile Glu Val Ala Ile Asp Glu Met Ser Lys Lys Val
                965                 970                 975
Ala Glu Leu Arg Gln Leu Cys Ser Ser Ala Glu Val Asp Met Ile
                980                 985                 990
Lys Leu Gln Leu Lys Leu Gln Gly Ser Val Ser Val Gln Val Asn
                995                1000                1005
Ala Gly Pro Leu Ala Tyr Ala Arg Ala Phe Leu Asp Asp Thr Asn
             1010                1015                1020
Thr Lys Arg Tyr Pro Asp Asn Lys Val Lys Leu Leu Lys Glu Val
             1025                1030                1035
Phe Arg Gln Phe Val Glu Ala Cys Gly Gln Ala Leu Ala Val Asn
             1040                1045                1050
Glu Arg Leu Ile Lys Glu Asp Gln Leu Glu Tyr Gln Glu Glu Met
             1055                1060                1065
Lys Ala Asn Tyr Arg Glu Met Ala Lys Glu Leu Ser Glu Ile Met
             1070                1075                1080
His Glu Gln Ile Cys Pro Leu Glu Asp Glu Asp Glu Arg Leu Thr
             1085                1090                1095
Glu Phe Pro Ser His Leu Gln Arg His Gln Trp Asp Ser Asn Lys
             1100                1105                1110
His Asn Gly Ser Arg Asp Asp Gln Leu Val Phe Gly Arg Val Ile
             1115                1120                1125
Thr Ser His Gly Pro Cys Val Gly Thr Cys Phe Val Ile Cys Lys
             1130                1135                1140
Leu Arg Met Leu Ser Lys Ala Asn His Trp Gly Asp Arg Ala Gln
             1145                1150                1155
Gly Gly Pro Arg Gly Arg Gly Glu Lys Gly Asn Lys Glu Gln Arg
             1160                1165                1170
Tyr Phe Leu Thr Asp Phe Leu
             1175
<210> 39
<211> 665
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1686305CD1

<400> 39
Met Thr Ser Ala Asn Lys Ala Ile Glu Leu Gln Leu Gln Val Lys
  1               5                  10                  15
Gln Asn Ala Glu Glu Leu Gln Asp Phe Met Arg Asp Leu Glu Asn
             20                  25                  30
Trp Glu Lys Asp Ile Lys Gln Lys Asp Met Glu Leu Arg Arg Gln
             35                  40                  45
Asn Gly Val Pro Glu Glu Asn Leu Pro Pro Ile Arg Asn Gly Asn
             50                  55                  60
Phe Arg Lys Lys Lys Lys Gly Lys Ala Lys Glu Ser Ser Lys Lys
             65                  70                  75
Thr Arg Glu Glu Asn Thr Lys Asn Arg Ile Lys Ser Tyr Asp Tyr
             80                  85                  90
Glu Ala Trp Ala Lys Leu Asp Val Asp Arg Ile Leu Asp Glu Leu
```

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                95                  100                 105
Asp Lys Asp Asp Ser Thr His Glu Ser Leu Ser Gln Glu Ser Glu
            110                 115                 120
Ser Glu Glu Asp Gly Ile His Val Asp Ser Gln Lys Ala Leu Val
        125                 130                 135
Leu Lys Glu Lys Gly Asn Lys Tyr Phe Lys Gln Gly Lys Tyr Asp
    140                 145                 150
Glu Ala Ile Asp Cys Tyr Thr Lys Gly Met Asp Ala Asp Pro Tyr
155                 160                 165
Asn Pro Val Leu Pro Thr Asn Arg Ala Ser Ala Tyr Phe Arg Leu
            170                 175                 180
Lys Lys Phe Ala Val Ala Glu Ser Asp Cys Asn Leu Ala Val Ala
        185                 190                 195
Leu Asn Arg Ser Tyr Thr Lys Ala Tyr Ser Arg Arg Gly Ala Ala
    200                 205                 210
Arg Phe Ala Leu Gln Lys Leu Glu Glu Ala Lys Lys Asp Tyr Glu
215                 220                 225
Arg Val Leu Glu Leu Glu Pro Asn Asn Phe Glu Ala Thr Asn Glu
            230                 235                 240
Leu Arg Lys Ile Ser Gln Ala Leu Ala Ser Lys Glu Asn Ser Tyr
        245                 250                 255
Pro Lys Glu Ala Asp Ile Val Ile Lys Ser Thr Glu Gly Glu Arg
    260                 265                 270
Lys Gln Ile Glu Ala Gln Gln Asn Lys Gln Gln Ala Ile Ser Glu
275                 280                 285
Lys Asp Arg Gly Asn Gly Phe Phe Lys Glu Gly Lys Tyr Glu Arg
            290                 295                 300
Ala Ile Glu Cys Tyr Thr Arg Gly Ile Ala Ala Asp Gly Ala Asn
305                 310                 315
Ala Leu Leu Pro Ala Asn Arg Ala Met Ala Tyr Leu Lys Ile Gln
            320                 325                 330
Lys Tyr Glu Glu Ala Glu Lys Asp Cys Thr Gln Ala Ile Leu Leu
        335                 340                 345
Asp Gly Ser Tyr Ser Lys Ala Phe Ala Arg Arg Gly Thr Ala Arg
    350                 355                 360
Thr Phe Leu Gly Lys Leu Asn Glu Ala Lys Gln Asp Phe Glu Thr
365                 370                 375
Val Leu Leu Leu Glu Pro Gly Asn Lys Gln Ala Val Thr Glu Leu
            380                 385                 390
Ser Lys Ile Lys Lys Glu Leu Ile Glu Lys Gly His Trp Asp Asp
        395                 400                 405
Val Phe Leu Asp Ser Thr Gln Arg Gln Asn Val Val Lys Pro Ile
    410                 415                 420
Asp Asn Pro Pro His Pro Gly Ser Thr Lys Pro Leu Lys Lys Val
425                 430                 435
Ile Ile Glu Glu Thr Gly Asn Leu Ile Gln Thr Ile Asp Val Pro
            440                 445                 450
Asp Ser Thr Thr Ala Ala Ala Pro Glu Asn Asn Pro Ile Asn Leu
        455                 460                 465
Ala Asn Val Ile Ala Ala Thr Gly Thr Thr Ser Lys Lys Asn Ser
    470                 475                 480
Ser Gln Asp Asp Leu Phe Pro Thr Ser Asp Thr Pro Arg Ala Lys
485                 490                 495
Val Leu Lys Ile Glu Glu Val Ser Asp Thr Ser Ser Leu Gln Pro
            500                 505                 510
Gln Ala Ser Leu Lys Gln Asp Val Cys Gln Ser Tyr Ser Glu Lys
        515                 520                 525
Met Pro Ile Glu Ile Glu Gln Lys Pro Ala Gln Phe Ala Thr Thr
    530                 535                 540
Val Leu Pro Pro Ile Pro Ala Asn Ser Phe Gln Leu Glu Ser Asp
545                 550                 555
Phe Arg Gln Leu Lys Ser Ser Pro Asp Met Leu Tyr Gln Tyr Leu
            560                 565                 570
Lys Gln Ile Glu Pro Ser Leu Tyr Pro Lys Leu Phe Gln Lys Asn
        575                 580                 585
Leu Asp Pro Asp Val Phe Asn Gln Ile Val Lys Ile Leu His Asp
    590                 595                 600
```

Phe Tyr Ile Glu Lys Glu Lys Pro Leu Leu Ile Phe Glu Ile Leu
605 610 615
Gln Arg Leu Ser Glu Leu Lys Arg Phe Asp Met Ala Val Met Phe
620 625 630
Met Ser Glu Thr Glu Lys Lys Ile Ala Arg Ala Leu Phe Asn His
635 640 645
Ile Asp Lys Ser Gly Leu Lys Asp Ser Ser Val Glu Glu Leu Lys
650 655 660
Lys Arg Tyr Gly Gly
665

<210> 40
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1688972CD1

<400> 40
Met Leu Asp Leu Gln Lys Gln Leu Gly Arg Phe Pro Gly Thr Phe
1 5 10 15
Val Gly Thr Thr Glu Pro Ala Ser Pro Pro Leu Ser Ser Thr Ser
20 25 30
Pro Thr Thr Ala Ala Ala Thr Met Pro Val Val Pro Ser Val Ala
35 40 45
Ser Leu Ala Pro Pro Gly Glu Ala Ser Leu Cys Leu Glu Glu Val
50 55 60
Ala Pro Pro Ala Ser Gly Thr Arg Lys Ala Arg Val Leu Tyr Asp
65 70 75
Tyr Glu Ala Ala Asp Ser Ser Glu Leu Ala Leu Leu Ala Asp Glu
80 85 90
Leu Ile Thr Val Tyr Ser Leu Pro Gly Met Asp Pro Asp Trp Leu
95 100 105
Ile Gly Glu Arg Gly Asn Lys Lys Gly Lys Val Pro Val Thr Tyr
110 115 120
Leu Glu Leu Leu Ser
125

<210> 41
<211> 366
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1812494CD1

<400> 41
Met Cys Tyr Phe Tyr Leu Gly Asp Lys Ile Lys Thr Ile Ser Phe
1 5 10 15
Gln Ala Phe Ile Leu Met His Leu Leu Leu Pro Ser Glu Tyr Ser
20 25 30
Leu Asp Gly Phe His Met Ser Gly Phe Ser Leu Gly Ser Gly Ser
35 40 45
Glu Gly Glu Asp Gly Phe Gln Val Glu Leu Glu Leu Val Glu Leu
50 55 60
Thr Val Gly Thr Leu Asp Leu Cys Glu Ser Glu Val Leu Pro Lys
65 70 75
Arg Arg Arg Arg Lys Arg Asn Lys Lys Glu Lys Ser Arg Asp Gln
80 85 90
Glu Ala Gly Ala His Arg Thr Leu Leu Gln Gln Thr Gln Glu Glu
95 100 105
Glu Pro Ser Thr Gln Ser Ser Gln Ala Val Ala Ala Pro Leu Gly
110 115 120
Pro Leu Leu Asp Glu Ala Lys Ala Pro Gly Gln Pro Glu Leu Trp
125 130 135
Asn Ala Leu Leu Ala Ala Cys Arg Ala Gly Asp Val Gly Val Leu

```
                  140                 145                 150
Lys Leu Gln Leu Ala Pro Ser Pro Ala Asp Pro Arg Val Leu Ser
                  155                 160                 165
Leu Leu Ser Ala Pro Leu Gly Ser Gly Gly Phe Thr Leu Leu His
                  170                 175                 180
Ala Ala Ala Ala Ala Gly Arg Gly Ser Val Val Arg Leu Leu Leu
                  185                 190                 195
Glu Ala Gly Ala Asp Pro Thr Val Gln Asp Ser Arg Ala Arg Pro
                  200                 205                 210
Pro Tyr Thr Val Ala Ala Asp Lys Ser Thr Arg Asn Glu Phe Arg
                  215                 220                 225
Arg Phe Met Glu Lys Asn Pro Asp Ala Tyr Asp Tyr Asn Lys Ala
                  230                 235                 240
Gln Val Pro Gly Pro Leu Thr Pro Glu Met Glu Ala Arg Gln Ala
                  245                 250                 255
Thr Arg Lys Arg Glu Gln Lys Ala Ala Arg Arg Gln Arg Glu Glu
                  260                 265                 270
Gln Gln Gln Arg Gln Gln Glu Gln Glu Glu Arg Glu Arg Glu Glu
                  275                 280                 285
Gln Arg Arg Phe Ala Ala Leu Ser Asp Arg Glu Lys Arg Ala Leu
                  290                 295                 300
Ala Ala Glu Arg Arg Leu Ala Ala Gln Leu Gly Ala Pro Thr Ser
                  305                 310                 315
Pro Ile Pro Asp Ser Ala Ile Val Asn Thr Arg Arg Cys Trp Ser
                  320                 325                 330
Cys Gly Ala Ser Leu Gln Gly Leu Thr Pro Phe His Tyr Leu Asp
                  335                 340                 345
Phe Ser Phe Cys Ser Thr Arg Cys Leu Gln Asp His Arg Arg Gln
                  350                 355                 360
Ala Gly Arg Pro Ser Ser
                  365

<210> 42
<211> 173
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2013853CD1

<400> 42
Met Ser Thr Met Gly Asn Glu Ala Ser Tyr Pro Ala Glu Met Cys
  1               5                  10                  15
Ser His Phe Asp Asn Asp Glu Ile Lys Arg Leu Gly Arg Arg Phe
                 20                  25                  30
Lys Lys Leu Asp Leu Asp Lys Ser Gly Ser Leu Ser Val Glu Glu
                 35                  40                  45
Phe Met Ser Leu Pro Glu Leu Arg His Asn Pro Leu Val Arg Arg
                 50                  55                  60
Val Ile Asp Val Phe Asp Thr Asp Gly Asp Gly Glu Val Asp Phe
                 65                  70                  75
Lys Glu Phe Ile Leu Gly Thr Ser Gln Phe Ser Val Lys Gly Asp
                 80                  85                  90
Glu Glu Gln Lys Leu Arg Phe Ala Phe Ser Ile Tyr Asp Met Asp
                 95                 100                 105
Lys Asp Gly Tyr Ile Ser Asn Gly Glu Leu Phe Gln Val Leu Lys
                110                 115                 120
Met Met Val Gly Asn Asn Leu Thr Asp Trp Gln Leu Gln Gln Leu
                125                 130                 135
Val Asp Lys Thr Ile Ile Ile Leu Asp Lys Asp Gly Asp Gly Lys
                140                 145                 150
Ile Ser Phe Glu Glu Phe Ser Ala Val Val Arg Asp Leu Glu Ile
                155                 160                 165
His Lys Lys Leu Val Leu Ile Val
                170

<210> 43
<211> 761
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<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2284925CD1

<400> 43
Met Arg Leu Thr Gln Asp Pro Ile Gln Val Leu Leu Ile Phe Ala
1 5 10 15
Lys Glu Asp Ser Gln Ser Asp Gly Phe Trp Trp Ala Cys Asp Arg
20 25 30
Ala Gly Tyr Arg Cys Asn Ile Ala Arg Thr Pro Glu Ser Ala Leu
35 40 45
Glu Cys Phe Leu Asp Lys His His Glu Ile Ile Val Ile Asp His
50 55 60
Arg Gln Thr Gln Asn Phe Asp Ala Glu Ala Val Cys Arg Ser Ile
65 70 75
Arg Ala Thr Asn Pro Ser Glu His Thr Val Ile Leu Ala Val Val
80 85 90
Ser Arg Val Ser Asp Asp His Glu Glu Ala Ser Val Leu Pro Leu
95 100 105
Leu His Ala Gly Phe Asn Arg Arg Phe Met Glu Asn Ser Ser Ile
110 115 120
Ile Ala Cys Tyr Asn Glu Leu Ile Gln Ile Glu His Gly Glu Val
125 130 135
Arg Ser Gln Phe Lys Leu Arg Ala Cys Asn Ser Val Phe Thr Ala
140 145 150
Leu Asp His Cys His Glu Ala Ile Glu Ile Thr Ser Asp Asp His
155 160 165
Val Ile Gln Tyr Val Asn Pro Ala Phe Glu Arg Met Met Gly Tyr
170 175 180
His Lys Gly Glu Leu Leu Gly Lys Glu Leu Ala Asp Leu Pro Lys
185 190 195
Ser Asp Lys Asn Arg Ala Asp Leu Leu Asp Thr Ile Asn Thr Cys
200 205 210
Ile Lys Lys Gly Lys Glu Trp Gln Gly Val Tyr Tyr Ala Arg Arg
215 220 225
Lys Ser Gly Asp Ser Ile Gln Gln His Val Lys Ile Thr Pro Val
230 235 240
Ile Gly Gln Gly Gly Lys Ile Arg His Phe Val Ser Leu Lys Lys
245 250 255
Leu Cys Cys Thr Thr Asp Asn Asn Lys Gln Ile His Lys Ile His
260 265 270
Arg Asp Ser Gly Asp Asn Ser Gln Thr Glu Pro His Ser Phe Arg
275 280 285
Tyr Lys Asn Arg Arg Lys Glu Ser Ile Asp Val Lys Ser Ile Ser
290 295 300
Ser Arg Gly Ser Asp Ala Pro Ser Leu Gln Asn Arg Arg Tyr Pro
305 310 315
Ser Met Ala Arg Ile His Ser Met Thr Ile Glu Ala Pro Ile Thr
320 325 330
Lys Val Ile Asn Ile Ile Asn Ala Ala Gln Glu Asn Ser Pro Val
335 340 345
Thr Val Ala Glu Ala Leu Asp Arg Val Leu Glu Ile Leu Arg Thr
350 355 360
Thr Glu Leu Tyr Ser Pro Gln Leu Gly Thr Lys Asp Glu Asp Pro
365 370 375
His Thr Ser Asp Leu Val Gly Gly Leu Met Thr Asp Gly Leu Arg
380 385 390
Arg Leu Ser Gly Asn Glu Tyr Val Phe Thr Lys Asn Val His Gln
395 400 405
Ser His Ser His Leu Ala Met Pro Ile Thr Ile Asn Asp Val Pro
410 415 420
Pro Cys Ile Ser Gln Leu Leu Asp Asn Glu Glu Ser Trp Asp Phe
425 430 435
Asn Ile Phe Glu Leu Glu Ala Ile Thr His Lys Arg Pro Leu Val

```
                440                 445                 450
Tyr Leu Gly Leu Lys Val Phe Ser Arg Phe Gly Val Cys Glu Phe
                455                 460                 465
Leu Asn Cys Ser Glu Thr Thr Leu Arg Ala Trp Phe Gln Val Ile
                470                 475                 480
Glu Ala Asn Tyr His Ser Ser Asn Ala Tyr His Asn Ser Thr His
                485                 490                 495
Ala Ala Asp Val Leu His Ala Thr Ala Phe Phe Leu Gly Lys Glu
                500                 505                 510
Arg Val Lys Gly Ser Leu Asp Gln Leu Asp Glu Val Ala Ala Leu
                515                 520                 525
Ile Ala Ala Thr Val His Asp Val Asp His Pro Gly Arg Thr Asn
                530                 535                 540
Ser Phe Leu Cys Asn Ala Gly Ser Glu Leu Ala Val Leu Tyr Asn
                545                 550                 555
Asp Thr Ala Val Leu Glu Ser His His Thr Ala Leu Ala Phe Gln
                560                 565                 570
Leu Thr Val Lys Asp Thr Lys Cys Asn Ile Phe Lys Asn Ile Asp
                575                 580                 585
Arg Asn His Tyr Arg Thr Leu Arg Gln Ala Ile Ile Asp Met Val
                590                 595                 600
Leu Ala Thr Glu Met Thr Lys His Phe Glu His Val Asn Lys Phe
                605                 610                 615
Val Asn Ser Ile Asn Lys Pro Met Ala Ala Glu Ile Glu Gly Ser
                620                 625                 630
Asp Cys Glu Cys Asn Pro Ala Gly Lys Asn Phe Pro Glu Asn Gln
                635                 640                 645
Ile Leu Ile Lys Arg Met Met Ile Lys Cys Ala Asp Val Ala Asn
                650                 655                 660
Pro Cys Arg Pro Leu Asp Leu Cys Ile Glu Trp Ala Gly Arg Ile
                665                 670                 675
Ser Glu Glu Tyr Phe Ala Gln Thr Asp Glu Glu Lys Arg Gln Gly
                680                 685                 690
Leu Pro Val Val Met Pro Val Phe Asp Arg Asn Thr Cys Ser Ile
                695                 700                 705
Pro Lys Ser Gln Ile Ser Phe Ile Asp Tyr Phe Ile Thr Asp Met
                710                 715                 720
Phe Asp Ala Trp Asp Ala Phe Ala His Leu Pro Ala Leu Met Gln
                725                 730                 735
His Leu Ala Asp Asn Tyr Lys His Trp Lys Thr Leu Asp Asp Leu
                740                 745                 750
Lys Cys Lys Ser Leu Arg Leu Pro Ser Asp Ser
                755                 760
```

<210> 44
<211> 249
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2376728CD1

```
<400> 44
Met Val Asp Arg Leu Ala Asn Ser Glu Ala Asn Thr Arg Arg Ile
  1               5                  10                  15
Ser Ile Val Glu Asn Cys Phe Gly Ala Ala Gly Gln Pro Leu Thr
             20                  25                  30
Ile Pro Gly Arg Val Leu Ile Gly Glu Gly Val Leu Thr Lys Leu
             35                  40                  45
Cys Arg Lys Lys Pro Lys Ala Arg Gln Phe Phe Leu Phe Asn Asp
             50                  55                  60
Ile Leu Val Tyr Gly Asn Ile Val Ile Gln Lys Lys Lys Tyr Asn
             65                  70                  75
Lys Gln His Ile Ile Pro Leu Glu Asn Val Thr Ile Asp Ser Ile
             80                  85                  90
Lys Asp Glu Gly Asp Leu Arg Asn Gly Trp Leu Ile Lys Thr Pro
             95                 100                 105
```

```
Thr Lys Ser Phe Ala Val Tyr Ala Ala Thr Ala Thr Glu Lys Ser
                110                 115                 120
Glu Trp Met Asn His Ile Asn Lys Cys Val Thr Asp Leu Leu Ser
                125                 130                 135
Lys Ser Gly Lys Thr Pro Ser Asn Glu His Ala Ala Val Trp Val
                140                 145                 150
Pro Asp Ser Glu Ala Thr Val Cys Met Arg Cys Gln Lys Ala Lys
                155                 160                 165
Phe Thr Pro Val Asn Arg Arg His His Cys Arg Lys Cys Gly Phe
                170                 175                 180
Val Val Cys Gly Pro Cys Ser Glu Lys Arg Phe Leu Leu Pro Ser
                185                 190                 195
Gln Ser Ser Lys Pro Val Arg Ile Cys Asp Phe Cys Tyr Asp Leu
                200                 205                 210
Leu Ser Ala Gly Asp Met Ala Thr Cys Gln Pro Ala Arg Ser Asp
                215                 220                 225
Ser Tyr Ser Gln Ser Leu Lys Ser Pro Leu Asn Asp Met Ser Asp
                230                 235                 240
Asp Asp Asp Asp Asp Asp Ser Ser Asp
                245
```

<210> 45
<211> 247
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2790762CD1

```
<400> 45
Met Glu Thr Asp Glu Ser Pro Ser Pro Leu Pro Cys Gly Pro Ala
  1               5                  10                  15
Gly Glu Ala Val Met Glu Ser Arg Ala Arg Pro Phe Gln Ala Leu
             20                  25                  30
Pro Arg Glu Gln Ser Pro Pro Pro Pro Leu Gln Thr Ser Ser Gly
         35                  40                  45
Ala Glu Val Met Asp Val Gly Ser Gly Gly Asp Gly Gln Ser Glu
     50                  55                  60
Leu Pro Ala Glu Asp Pro Phe Asn Phe Tyr Gly Ala Ser Leu Leu
 65                  70                  75                  80
Ser Lys Gly Ser Phe Ser Lys Gly Arg Leu Leu Ile Asp Pro Asn
                 85                  90                  95
Cys Ser Gly His Ser Pro Arg Thr Ala Arg His Ala Pro Ala Val
            100                 105                 110
Arg Lys Phe Ser Pro Asp Leu Lys Leu Leu Lys Asp Val Lys Ile
        115                 120                 125
Ser Val Ser Phe Thr Glu Ser Cys Arg Ser Lys Asp Arg Lys Val
    130                 135                 140
Leu Tyr Thr Gly Ala Glu Arg Asp Val Arg Ala Glu Cys Gly Leu
145                 150                 155                 160
Leu Leu Ser Pro Val Ser Gly Asp Val His Ala Cys Pro Phe Gly
                165                 170                 175
Gly Ser Val Gly Asp Gly Val Gly Ile Gly Gly Glu Ser Ala Asp
            180                 185                 190
Lys Lys Asp Glu Glu Asn Glu Leu Asp Gln Glu Lys Arg Val Glu
        195                 200                 205
Tyr Ala Val Leu Asp Glu Leu Glu Asp Phe Thr Asp Asn Leu Glu
    210                 215                 220
Leu Asp Glu Glu Gly Ala Gly Gly Phe Thr Ala Lys Ala Ile Val
225                 230                 235                 240
Gln Arg Asp Arg Val Asp Glu Glu Ala Leu Asn Phe Pro Tyr Glu
                245                 250                 255
Val Cys Trp Gln Pro Leu Leu
            260
```

<210> 46
<211> 316
<212> PRT

<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2869164CD1

<400> 46
Met Ala Glu Ala Ala Leu Glu Ala Val Arg Ser Glu Leu Arg Glu
1 5 10 15
Phe Pro Ala Ala Ala Arg Glu Leu Cys Val Pro Leu Ala Val Pro
20 25 30
Tyr Leu Asp Lys Pro Pro Thr Pro Leu His Phe Tyr Arg Asp Trp
35 40 45
Val Cys Pro Asn Arg Pro Cys Ile Ile Arg Asn Ala Leu Gln His
50 55 60
Trp Pro Ala Leu Gln Lys Trp Ser Leu Pro Tyr Phe Arg Ala Thr
65 70 75
Val Gly Ser Thr Glu Val Ser Val Ala Val Thr Pro Asp Gly Tyr
80 85 90
Ala Asp Ala Val Arg Gly Asp Arg Phe Met Met Pro Ala Glu Arg
95 100 105
Arg Leu Pro Leu Ser Phe Val Leu Asp Val Leu Glu Gly Arg Ala
110 115 120
Gln His Pro Gly Val Leu Tyr Val Gln Lys Gln Cys Ser Asn Leu
125 130 135
Pro Ser Glu Leu Pro Gln Leu Leu Pro Asp Leu Glu Ser His Val
140 145 150
Pro Trp Ala Ser Glu Ala Leu Gly Lys Met Pro Asp Ala Val Asn
155 160 165
Phe Trp Leu Gly Glu Ala Ala Ala Val Thr Ser Leu His Lys Asp
170 175 180
His Tyr Glu Asn Leu Tyr Cys Val Val Ser Gly Glu Lys His Phe
185 190 195
Leu Phe His Pro Pro Ser Asp Arg Pro Phe Ile Pro Tyr Glu Leu
200 205 210
Tyr Thr Pro Ala Thr Tyr Gln Leu Thr Glu Glu Gly Thr Phe Lys
215 220 225
Val Val Asp Glu Glu Ala Met Glu Lys Val Pro Trp Ile Pro Leu
230 235 240
Asp Pro Leu Ala Pro Asp Leu Ala Arg Tyr Pro Ser Tyr Ser Gln
245 250 255
Ala Gln Ala Leu Arg Cys Thr Val Arg Ala Gly Glu Met Leu Tyr
260 265 270
Leu Pro Ala Leu Trp Phe His His Val Gln Gln Ser Gln Gly Cys
275 280 285
Ile Ala Val Asn Phe Trp Tyr Asp Met Glu Tyr Asp Leu Lys Tyr
290 295 300
Ser Tyr Phe Gln Leu Leu Asp Ser Leu Thr Lys Ala Ser Gly Leu
305 310 315
Asp

<210> 47
<211> 334
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3317629CD1

<400> 47
Met Thr Arg Ser Leu Phe Lys Gly Asn Phe Trp Ser Ala Asp Ile
1 5 10 15
Leu Ser Thr Ile Gly Tyr Asp Asn Ile Ile Gln His Leu Asn Asn
20 25 30
Gly Arg Lys Asn Cys Lys Glu Phe Glu Asp Phe Leu Lys Glu Arg
35 40 45

Ala Ala Ile Glu Glu Arg Tyr Gly Lys Asp Leu Leu Asn Leu Ser
50 55 60
Arg Lys Lys Pro Cys Gly Gln Ser Glu Ile Asn Thr Leu Lys Arg
65 70 75
Ala Leu Glu Val Phe Lys Gln Gln Val Asp Asn Val Ala Gln Cys
80 85 90
His Ile Gln Leu Ala Gln Ser Leu Arg Glu Glu Ala Arg Lys Met
95 100 105
Glu Glu Phe Arg Glu Lys Gln Lys Leu Gln Arg Lys Lys Thr Glu
110 115 120
Leu Ile Met Asp Ala Ile His Lys Gln Lys Ser Leu Gln Phe Lys
125 130 135
Lys Thr Met Asp Ala Lys Lys Asn Tyr Glu Gln Lys Cys Arg Asp
140 145 150
Lys Asp Glu Ala Glu Gln Ala Val Ser Arg Ser Ala Asn Leu Val
155 160 165
Asn Pro Lys Gln Gln Glu Lys Leu Phe Val Lys Leu Ala Thr Ser
170 175 180
Lys Thr Ala Val Glu Asp Ser Asp Lys Ala Tyr Met Leu His Ile
185 190 195
Gly Thr Leu Asp Lys Val Arg Glu Glu Trp Gln Ser Glu His Ile
200 205 210
Lys Ala Cys Glu Ala Phe Glu Ala Gln Glu Cys Glu Arg Ile Asn
215 220 225
Phe Phe Arg Asn Ala Leu Trp Leu His Val Asn Gln Leu Ser Gln
230 235 240
Gln Cys Val Thr Ser Asp Glu Met Tyr Glu Gln Val Arg Lys Ser
245 250 255
Leu Glu Met Cys Ser Ile Gln Arg Asp Ile Glu Tyr Phe Val Asn
260 265 270
Gln Arg Lys Thr Gly Gln Ile Pro Pro Ala Pro Ile Met Tyr Glu
275 280 285
Asn Phe Tyr Ser Ser Gln Lys Asn Ala Val Pro Ala Gly Lys Ala
290 295 300
Thr Gly Pro Asn Leu Ala Arg Arg Gly Pro Leu Pro Ile Pro Lys
305 310 315
Ser Ser Pro Asp Asp Pro Asn Tyr Ser Leu Val Asp Asp Tyr Ser
320 325 330
Leu Leu Tyr Gln

<210> 48
<211> 113
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3870488CD1

<400> 48
Met Asp Pro Lys Leu Leu Lys Gln Leu Arg Lys Ala Glu Lys Ala
1 5 10 15
Glu Arg Glu Phe Arg Lys Lys Phe Lys Phe Glu Gly Glu Ile Val
20 25 30
Val His Thr Lys Met Met Ile Asp Pro Asn Ala Lys Thr Arg Arg
35 40 45
Gly Gly Gly Lys His Leu Gly Ile Arg Arg Gly Glu Ile Leu Glu
50 55 60
Val Ile Glu Phe Thr Ser Asn Glu Glu Met Leu Cys Arg Asp Pro
65 70 75
Lys Gly Lys Tyr Gly Tyr Val Pro Arg Thr Ala Leu Leu Pro Leu
80 85 90
Glu Thr Glu Val Tyr Asp Asp Val Asp Phe Cys Asp Pro Leu Glu
95 100 105
Asn Gln Pro Leu Pro Leu Gly Arg
110

<210> 49

<211> 264
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3886318CD1

<400> 49
Met Leu Gly Ala Glu Thr Glu Glu Lys Leu Phe Asp Ala Pro Leu
1 5 10 15
Ser Ile Ser Lys Arg Glu Gln Leu Glu Gln Gln Val Pro Glu Asn
20 25 30
Tyr Phe Tyr Val Pro Asp Leu Gly Gln Val Pro Glu Ile Asp Val
35 40 45
Pro Ser Tyr Leu Pro Asp Leu Pro Gly Ile Ala Asn Asp Leu Met
50 55 60
Tyr Ile Ala Asp Leu Gly Pro Gly Ile Ala Pro Ser Ala Pro Gly
65 70 75
Thr Ile Pro Glu Leu Pro Thr Phe His Thr Glu Val Ala Glu Pro
80 85 90
Leu Lys Ala Asp Leu Gln Asp Gly Val Leu Thr Pro Pro Pro Pro
95 100 105
Pro Pro Pro Pro Pro Pro Ala Pro Glu Val Leu Ala Ser Ala Pro
110 115 120
Pro Leu Pro Pro Ser Thr Ala Ala Pro Val Gly Gln Gly Ala Arg
125 130 135
Gln Asp Asp Ser Ser Ser Ser Ala Ser Pro Ser Val Gln Gly Ala
140 145 150
Pro Arg Glu Val Val Asp Pro Ser Gly Gly Arg Ala Thr Leu Leu
155 160 165
Glu Ser Ile Arg Gln Ala Gly Gly Ile Gly Lys Ala Lys Leu Arg
170 175 180
Ser Met Lys Glu Arg Lys Leu Glu Lys Lys Gln Gln Lys Glu Gln
185 190 195
Glu Gln Val Arg Ala Thr Ser Gln Gly Gly His Leu Met Ser Asp
200 205 210
Leu Phe Asn Lys Leu Val Met Arg Arg Lys Gly Ile Ser Gly Lys
215 220 225
Gly Pro Gly Ala Gly Glu Gly Pro Gly Gly Ala Phe Ala Arg Val
230 235 240
Ser Asp Ser Ile Pro Pro Leu Pro Pro Pro Gln Gln Pro Gln Ala
245 250 255
Glu Glu Asp Glu Asp Asp Trp Glu Ser
260

<210> 50
<211> 185
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 4043934CD1

<400> 50
Met Gly Gln Cys Leu Arg Tyr Gln Met His Trp Glu Asp Leu Glu
1 5 10 15
Glu Tyr Gln Ala Leu Thr Phe Leu Thr Arg Asn Glu Ile Leu Cys
20 25 30
Ile His Asp Thr Phe Leu Lys Leu Cys Pro Pro Gly Lys Tyr Tyr
35 40 45
Lys Glu Ala Thr Leu Thr Met Asp Gln Val Ser Ser Leu Pro Ala
50 55 60
Leu Arg Val Asn Pro Phe Arg Asp Arg Ile Cys Arg Val Phe Ser
65 70 75
His Lys Gly Met Phe Ser Phe Glu Asp Val Leu Gly Met Ala Ser
80 85 90

```
Val Phe Ser Glu Gln Ala Cys Pro Ser Leu Lys Ile Glu Tyr Ala
                 95                  100                 105
Phe Arg Ile Tyr Asp Phe Asn Glu Asn Gly Phe Ile Asp Glu Glu
                110                 115                 120
Asp Leu Gln Arg Ile Ile Leu Arg Leu Leu Asn Ser Asp Asp Met
                125                 130                 135
Ser Glu Asp Leu Leu Met Asp Leu Thr Asn His Val Leu Ser Glu
                140                 145                 150
Ser Asp Leu Asp Asn Asp Asn Met Leu Ser Phe Ser Glu Phe Glu
                155                 160                 165
His Ala Met Ala Lys Ser Pro Asp Phe Met Tyr Ser Phe Arg Ile
                170                 175                 180
Arg Phe Trp Gly Cys
                185
```

<210> 51
<211> 72
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 4371445CD1

```
<400> 51
Met Phe Thr Ile Ile Phe Pro Val Cys Lys Asn Ser Met Pro Val
  1               5                  10                  15
Lys Lys Thr Asp Thr Asp Arg Ala Leu Ser Leu Leu Glu Glu Tyr
                 20                  25                  30
Cys Lys Lys Leu Arg Lys Pro Glu Glu Gln Leu Leu Lys Asn Ala
                 35                  40                  45
Val Lys Lys Val Met Gly Ile Phe Lys Ser Ser Leu Phe Gln Ala
                 50                  55                  60
Leu Leu Gly Met Tyr Tyr Glu Ser Tyr Ser Ser Phe
                 65                  70
```

<210> 52
<211> 434
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 5527925CD1

```
<400> 52
Met Ala Ala Ala Ala Gly Ser Cys Ala Arg Val Ala Ala Trp Gly
  1               5                  10                  15
Gly Lys Leu Arg Arg Gly Leu Ala Val Ser Arg Gln Ala Val Arg
                 20                  25                  30
Ser Pro Gly Pro Leu Ala Ala Ala Val Ala Gly Ala Ala Leu Ala
                 35                  40                  45
Gly Ala Gly Ala Ala Trp His His Ser Arg Val Ser Val Ala Ala
                 50                  55                  60
Arg Asp Gly Ser Phe Thr Val Ser Ala Gln Lys Asn Val Glu His
                 65                  70                  75
Gly Ile Ile Tyr Ile Gly Lys Pro Ser Leu Arg Lys Gln Arg Phe
                 80                  85                  90
Met Gln Phe Ser Ser Leu Glu His Glu Gly Glu Tyr Tyr Met Thr
                 95                 100                 105
Pro Arg Asp Phe Leu Phe Ser Val Met Phe Glu Gln Met Glu Arg
                110                 115                 120
Lys Thr Ser Val Lys Lys Leu Thr Lys Lys Asp Ile Glu Asp Thr
                125                 130                 135
Leu Ser Gly Ile Gln Thr Ala Gly Cys Gly Ser Thr Phe Phe Arg
                140                 145                 150
Asp Leu Gly Asp Lys Gly Leu Ile Ser Tyr Thr Glu Tyr Leu Phe
                155                 160                 165
Leu Leu Thr Ile Leu Thr Lys Pro His Ser Gly Phe His Val Ala
```

```
                170                 175                 180
Phe Lys Met Leu Asp Thr Asp Gly Asn Glu Met Ile Glu Lys Arg
                185                 190                 195
Glu Phe Phe Lys Leu Gln Lys Ile Ile Ser Lys Gln Asp Asp Leu
                200                 205                 210
Met Thr Val Lys Thr Asn Glu Thr Gly Tyr Gln Glu Ala Ile Val
                215                 220                 225
Lys Glu Pro Glu Ile Asn Thr Thr Leu Gln Met Arg Phe Phe Gly
                230                 235                 240
Lys Arg Gly Gln Arg Lys Leu His Tyr Lys Glu Phe Arg Arg Phe
                245                 250                 255
Met Glu Asn Leu Gln Thr Glu Ile Gln Glu Met Glu Phe Leu Gln
                260                 265                 270
Phe Ser Lys Gly Leu Ser Phe Met Arg Lys Glu Asp Phe Ala Glu
                275                 280                 285
Trp Leu Leu Phe Phe Thr Asn Thr Glu Asn Lys Asp Ile Tyr Trp
                290                 295                 300
Lys Asn Val Arg Glu Lys Leu Ser Ala Gly Glu Ser Ile Ser Leu
                305                 310                 315
Asp Glu Phe Lys Ser Phe Cys His Phe Thr Thr His Leu Glu Asp
                320                 325                 330
Phe Ala Ile Ala Met Gln Met Phe Ser Leu Ala His Arg Pro Val
                335                 340                 345
Arg Leu Ala Glu Phe Lys Arg Ala Val Lys Val Ala Thr Gly Gln
                350                 355                 360
Glu Leu Ser Asn Asn Ile Leu Asp Thr Val Phe Lys Ile Phe Asp
                365                 370                 375
Leu Asp Gly Asp Glu Cys Leu Ser His Glu Glu Phe Leu Gly Val
                380                 385                 390
Leu Lys Asn Arg Met His Arg Gly Leu Trp Val Pro Gln His Gln
                395                 400                 405
Ser Ile Gln Glu Tyr Trp Lys Cys Val Lys Lys Glu Ser Ile Lys
                410                 415                 420
Gly Val Lys Glu Val Trp Lys Gln Ala Gly Lys Gly Leu Phe
                425                 430
```

<210> 53
<211> 1629
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 129042CB1

<400> 53

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gcgacctgta tgaggaggag gaggaggagg atgtgaagat ggcggacgtg cagatgctgc 60
tggaagagga aatcccgggg ggccgccggg ccctcttcga cagctacaca aatctggaac 120
gggtggccga ttactgcgag aacaactaca tacagtcagc agataagcag agagccctag 180
aagaaaccaa agcctacacc acccaatcct tagcaagtgt tgcctatctg ataaacacct 240
tggccaacaa tgtcctgcag atgctggata tccaggcatc ccagctacga aggatggaat 300
cttcaatcaa tcatatttca caaacagttg atattcataa agagaaagtt gcaagaagag 360
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<211> 1156
<212> DNA
<213> Homo sapiens

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<221> misc_feature
<223> Incyte ID No: 4155412CB1

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<211> 1981
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<213> Homo sapiens

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<213> Homo sapiens

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<223> Incyte ID No: 5676581CB1

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<210> 71
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<211> 1772
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte ID No: 034159CB1

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<211> 1488
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 129023CB1

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<211> 2430
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte ID No: 1358940CB1

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<213> Homo sapiens

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<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1728263CB1

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<210> 76
<211> 1448
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1867626CB1

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<211> 1538
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte ID No: 1990126CB1

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<211> 998
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2104180CB1

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<211> 1086
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte ID No: 2122241CB1

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<210> 80
<211> 2323
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2580428CB1

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<210> 81
<211> 669
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3397189CB1

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<210> 82
<211> 1606
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte ID No: 4881249CB1

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<210> 83
<211> 1980
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 431871CB1

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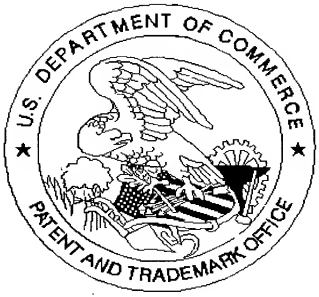

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